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(54) Title: EXTENDED cDNAs FOR SECRETED PROTEINS

(57) Abstract

The sequences of extended cDNAs encoding secreted proteins are disclosed. The extended cDNAs can be used to express secreted proteins or portions thereof or to obtain antibodies capable of specifically binding to the secreted proteins. The extended cDNAs may also be used in diagnostic, forensic, gene therapy, and chromosome mapping procedures. The extended cDNAs may also be used to design expression vectors and secretion vectors.

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EXTENDED cDNAS for secreted proteins

The present application relates to extended cONAs which were disclosed in several United States Provisional Patent Applications. Table I lists the SEQ IO Nos. of the extended cONAs in the present application, the SEQ IO Nos. of the identical or nearly identical extended cONAs in the provisional applications, and the identities of the provisional applications in which the extended cONAs were disclosed.

Background of the Invention

The estimated 50,000-100,000 genes scattered along the human chromosomes offer tremendous promise for the understanding, diagnosis, and treatment of human diseases. In addition, probes capable of specifically hybridizing to loci distributed throughout the human genome find applications in the construction of high resolution chromosome maps and in the identification of individuals.

In the past, the characterization of even a single human gene was a painstaking process, requiring years of effort. Recent developments in the areas of cloning vectors, DNA sequencing, and computer technology have merged to greatly accelerate the rate at which human genes can be isolated, sequenced, mapped, and characterized. Cloning vectors such as yeast artificial chromosomes (YACs) and bacterial artificial chromosomes (BACs) are able to accept DNA inserts ranging from 300 to 1000 kilobases (kb) or 100-400 kb in length respectively, thereby facilitating the manipulation and ordering of DNA sequences distributed over great distances on the human chromosomes. Automated DNA sequencing machines permit the rapid sequencing of human genes. Bioinformatics software enables the comparison of nucleic acid and protein sequences, thereby assisting in the characterization of human gene products.

Currently, two different approaches are being pursued for identifying and characterizing the genes distributed along the human genome. In one approach, large fragments of genomic DNA are isolated, cloned, and sequenced. Potential open reading frames in these genomic sequences are identified using bio-informatics software. However, this approach entails sequencing large stretches of human DNA which do not encode proteins in order to find the protein encoding sequences scattered throughout the genome. In addition to requiring extensive sequencing, the bio-informatics software may mischaracterize the genomic sequences obtained. Thus, the software may produce-false positives in which non-coding DNA is mischaracterized as coding DNA or false negatives in which coding DNA is mislabeled as non-coding DNA.

An alternative approach takes a more direct route to identifying and characterizing human genes. In this approach, complementary DNAs (cDNAs) are synthesized from isolated messenger RNAs (mRNAs) which encode human proteins. Using this approach, sequencing is only performed on DNA which is derived from protein coding portions of the genome. Often, only short stretches of the cDNAs are sequenced to obtain sequences called expressed sequence tags (ESTs). The ESTs may then be used to isolate or purify extended cDNAs which include sequences adjacent to the EST sequences. The extended cDNAs may contain all of the sequence of the EST which was used to obtain them or only a portion of the sequence of the EST which was used to obtain them. In addition, the extended cDNAs may contain the full coding sequence of the gene from which the EST was derived or, alternatively, the extended cDNAs may include

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portions of the coding sequence of the gene from which the EST was derived. It will be appreciated that there may be several extended cDNAs which include the EST sequence as a result of alternate splicing or the activity of alternative promoters.

In the past, the short EST sequences which could be used to isolate or purify extended cDNAs were often 5 obtained from oligo-dT primed cDNA libraries. Accordingly, they mainly corresponded to the 3' untranslated region of the mRNA. In part, the prevalence of EST sequences derived from the 3' end of the mRNA is a result of the fact that typical techniques for obtaining cDNAs, are not well suited for isolating cDNA sequences derived from the 5' ends of mRNAs. (Adams et al., *Nature* 377:174, 1996, Hillier et al., *Genome Res.* 6:807-828, 1996).

In addition, in those reported instances where longer cDNA sequences have been obtained, the reported 10 sequences typically correspond to coding sequences and do not include the full 5' untranslated region of the mRNA from which the cDNA is derived. Such incomplete sequences may not include the first exon of the mRNA, particularly in situations where the first exon is short. Furthermore, they may not include some exons, often short ones, which are located upstream of splicing sites. Thus, there is a need to obtain sequences derived from the 5' ends of mRNAs which can be used to obtain extended cDNAs which may include the 5' sequences contained in the 5' ESTs.

While many sequences derived from human chromosomes have practical applications, approaches based on the identification and characterization of those chromosomal sequences which encode a protein product are particularly relevant to diagnostic and therapeutic uses. Of the 50,000-100,000 protein coding genes, those genes encoding proteins which are secreted from the cell in which they are synthesized, as well as the secreted proteins themselves, are particularly valuable as potential therapeutic agents. Such proteins are often involved in cell to cell communication and 20 may be responsible for producing a clinically relevant response in their target cells.

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In fact, several secretory proteins, including tissue plasminogen activator, G-CSF, GM-CSF, erythropoietin, human growth hormone, insulin, interferon- α , interferon- β , interferon- γ , and interleukin-2, are currently in clinical use. These proteins are used to treat a wide range of conditions, including acute myocardial infarction, acute ischemic stroke, anemia, diabetes, growth hormone deficiency, hepatitis, kidney carcinoma, chemotherapy induced neutropenia and 25 multiple sclerosis. For these reasons, extended cDNAs encoding secreted proteins or portions thereof represent a particularly valuable source of therapeutic agents. Thus, there is a need for the identification and characterization of secreted proteins and the nucleic acids encoding them.

In addition to being therapeutically useful themselves, secretory proteins include short peptides, called signal peptides, at their amino termini which direct their secretion. These signal peptides are encoded by the signal sequences 30 located at the 5' ends of the coding sequences of genes encoding secreted proteins. Because these signal peptides will direct the extracellular secretion of any protein to which they are operably linked, the signal sequences may be exploited to direct the efficient secretion of any protein by operably linking the signal sequences to a gene encoding the protein for which secretion is desired. This may prove beneficial in gene therapy strategies in which it is desired to deliver a particular gene product to cells other than the cell in which it is produced. Signal sequences encoding signal peptides

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also find application in simplifying protein purification techniques. In such applications, the extracellular secretion of the desired protein greatly facilitates purification by reducing the number of undesired proteins from which the desired protein must be selected. Thus, there exists a need to identify and characterize the 5' portions of the genes for secretory proteins which encode signal peptides.

Public information on the number of human genes for which the promoters and upstream regulatory regions have been identified and characterized is quite limited. In part, this may be due to the difficulty of isolating such regulatory sequences. Upstream regulatory sequences such as transcription factor binding sites are typically too short to be utilized as probes for isolating promoters from human genomic libraries. Recently, some approaches have been developed to isolate human promoters. One of them consists of making a CpG island library (Cross, S.H. et al.,

Purification of CpG Islands using a Methylated DNA Binding Column, Nature Genetics 6: 236-244 (1994)). The second consists of isolating human genomic DNA sequences containing Spel binding sites by the use of Spel binding protein. (Mortlock et al., Genome Res. 6:327-335, 1996). Both of these approaches have their limits due to a lack of specificity or of comprehensiveness.

5' ESTs and extended cDNAs obtainable therefrom may be used to efficiently identify and isolate upstream regulatory regions which control the location, developmental stage, rate, and quantity of protein synthesis, as well as the stability of the mRNA. (Theil et al., BioFactors 4:87-93, (1993). Once identified and characterized, these regulatory regions may be utilized in gene therapy or protein purification schemes to obtain the desired amount and locations of protein synthesis or to inhibit, reduce, or prevent the synthesis of undesirable gene products.

In addition, ESTs containing the 5' ends of secretory protein genes or extended cDNAs which include
sequences adjacent to the sequences of the ESTs may include sequences useful as probes for chromosome mapping and
the identification of individuals. Thus, there is a need to identify and characterize the sequences upstream of the 5'
coding sequences of genes encoding secretory proteins.

Summary of the Invention

The present invention relates to purified, isolated, or recombinant extended cDNAs which encode secreted proteins or fragments thereof. Preferably, the purified, isolated or recombinant cDNAs contain the entire open reading frame of their corresponding mRNAs, including a start codon and a stop codon. For example, the extended cDNAs may include nucleic acids encoding the signal peptide as well as the mature protein. Alternatively, the extended cDNAs may contain a fragment of the open reading frame. In some embodiments, the fragment may encode only the sequence of the mature protein. Alternatively, the fragment may encode only a portion of the mature protein. A further aspect of the present invention is a nucleic acid which encodes the signal peptide of a secreted protein.

The present extended cDNAs were obtained using ESTs which include sequences derived from the authentic 5' ends of their corresponding mRNAs. As used herein the terms "EST" or "5' EST" refer to the short cDNAs which were used to obtain the extended cDNAs of the present invention. As used herein, the term "extended cDNA" refers to the cDNAs which include sequences adjacent to the 5' EST used to obtain them. The extended cDNAs may contain all or a

portion of the sequence of the EST which was used to obtain them. The term "corresponding mRNA" refers to the mRNA which was the template for the cDNA synthesis which produced the 5' EST. As used herein, the term "purified" does not require absolute purity; rather, it is intended as a relative definition. Individual extended cDNA clones isolated from a cDNA library have been conventionally purified to electrophoretic homogeneity. The sequences obtained from these clones could not be obtained directly either from the library or from total human DNA. The extended cDNA clones are not naturally occurring as such, but rather are obtained via manipulation of a partially purified naturally occurring substance (messenger RNA). The conversion of mRNA into a cDNA library involves the creation of a synthetic substance (cDNA) and pure individual cDNA clones can be isolated from the synthetic library by clonal selection. Thus, creating a cDNA library from messenger RNA and subsequently isolating individual clones from that library results in an approximately 10⁴·10⁶ fold purification of the native message. Purification of starting material or natural material to at least one order of magnitude, preferably two or three orders, and more preferably four or five orders of magnitude is expressly contemplated.

As used herein, the term "isolated" requires that the material be removed from its original environment (e.g., the natural environment if it is naturally occurring). For example, a naturally-occurring polynucleotide present in a living animal is not isolated, but the same polynucleotide, separated from some or all of the coexisting materials in the natural system, is isolated.

As used herein, the term "recombinant" means that the extended cDNA is adjacent to "backbone" nucleic acid to which it is not adjacent in its natural environment. Additionally, to be "enriched" the extended cDNAs will represent 5% or more of the number of nucleic acid inserts in a population of nucleic acid backbone molecules. Backbone molecules according to the present invention include nucleic acids such as expression vectors, self-replicating nucleic acids, viruses, integrating nucleic acids, and other vectors or nucleic acids used to maintain or manipulate a nucleic acid insert of interest. Preferably, the enriched extended cDNAs represent 15% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. More preferably, the enriched extended cDNAs represent 50% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. In a highly preferred embodiment, the enriched extended cDNAs represent 90% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. "Stringent", "moderate," and "low" hybridization conditions are as defined in Example 29.

Unless otherwise indicated, a "complementary" sequence is fully complementary. Thus, extended cDNAs encoding secreted polypeptides or fragments thereof which are present in cDNA libraries in which one or more extended cDNAs encoding secreted polypeptides or fragments thereof make up 5% or more of the number of nucleic acid inserts in the backbone molecules are "enriched recombinant extended cDNAs" as defined herein. Likewise, extended cDNAs encoding secreted polypeptides or fragments thereof which are in a population of plasmids in which one or more extended cDNAs of the present invention have been inserted such that they represent 5% or more of the number of inserts in the plasmid backbone are "enriched recombinant extended cDNAs" as defined herein. However, extended

cDNAs encoding secreted polypeptides or fragments thereof which are in cDNA libraries in which the extended cDNAs encoding secreted polypeptides or fragments thereof constitute less than 5% of the number of nucleic acid inserts in the population of backbone molecules, such as libraries in which backbone molecules having a cDNA insert encoding a secreted polypeptide are extremely rare, are not "enriched recombinant extended cDNAs."

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In particular, the present invention relates to extended cDNAs which were derived from genes encoding secreted proteins. As used herein, a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal peptides in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g. soluble proteins), or partially (e.g. receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are 10 transported across the membrane of the endoplasmic reticulum.

Extended cDNAs encoding secreted proteins may include nucleic acid sequences, called signal sequences, which encode signal puptides which direct the extracellular secretion of the proteins encoded by the extended cDNAs. Generally, the signal peptides are located at the amino termini of secreted proteins.

Secreted proteins are translated by ribosomes associated with the "rough" endoplasmic reticulum. Generally, 15 secreted proteins are co-translationally transferred to the membrane of the endoplasmic reticulum. Association of the ribosome with the endoplasmic reticulum during translation of secreted proteins is mediated by the signal peptide. The signal peptide is typically cleaved following its co-translational entry into the endoplasmic reticulum. After delivery to the endoplasmic reticulum, secreted proteins may proceed through the Golgi apparatus. In the Golgi apparatus, the proteins may undergo post-translational modification before entering secretory vesicles which transport them across the 20 cell membrane.

The extended cDNAs of the present invention have several important applications. For example, they may be used to express the entire secreted protein which they encode. Alternatively, they may be used to express portions of the secreted protein. The portions may comprise the signal peptides encoded by the extended cDNAs or the mature proteins encoded by the extended cDNAs (i.e. the proteins generated when the signal peptide is cleaved off). The 25 portions may also comprise polypeptides having at least 10 consecutive amino acids encoded by the extended cDNAs. Alternatively, the portions may comprise at least 15 consecutive amino acids encoded by the extended cDNAs. In some embodiments, the portions may comprise at least 25 consecutive amino acids encoded by the extended cDNAs. In other embodiments, the portions may comprise at least 40 amino acids encoded by the extended cDNAs.

Antibodies which specifically recognize the entire secreted proteins encoded by the extended cDNAs or 30 fragments thereof having at least 10 consecutive amino acids, at least 15 consecutive amino acids, at least 25 consecutive amino acids, or at least 40 consecutive amino acids may also be obtained as described below. Antibodies which specifically recognize the mature protein generated when the signal peptide is cleaved may also be obtained as described below. Similarly, antibodies which specifically recognize the signal peptides encoded by the extended cDNAs may also be obtained.

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In some embodiments, the extended cDNAs include the signal sequence. In other embodiments, the extended cDNAs may include the full coding sequence for the mature protein (i.e. the protein generated when the signal polypeptide is cleaved off). In addition, the extended cDNAs may include regulatory regions upstream of the translation start site or downstream of the stop codon which control the amount, location, or developmental stage of gene expression. As discussed above, secreted proteins are therapeutically important. Thus, the proteins expressed from the cDNAs may be useful in treating or controlling a variety of human conditions. The extended cDNAs may also be used to obtain the corresponding genomic DNA. The term "corresponding genomic DNA" refers to the genomic DNA which encodes mRNA which includes the sequence of one of the strands of the extended cDNA in which thymidine residues in the sequence of the extended cDNA are replaced by uracil residues in the mRNA.

The extended cDNAs or genomic DNAs obtained therefrom may be used in forensic procedures to identify individuals or in diagnostic procedures to identify individuals having genetic diseases resulting from abnormal expression of the genes corresponding to the extended cDNAs. In addition, the present invention is useful for constructing a high resolution map of the human chromosomes.

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The present invention also relates to secretion vectors capable of directing the secretion of a protein of
interest. Such vectors may be used in gene therapy strategies in which it is desired to produce a gene product in one cell which is to be delivered to another location in the body. Secretion vectors may also facilitate the purification of desired proteins.

The present invention also relates to expression vectors capable of directing the expression of an inserted gene in a desired spatial or temporal manner or at a desired level. Such vectors may include sequences upstream of the extended cDNAs such as promoters or upstream regulatory sequences.

In addition, the present invention may also be used for gene therapy to control or treat genetic diseases. Signal peptides may also be fused to heterologous proteins to direct their extracellular secretion.

One embodiment of the present invention is a purified or isolated nucleic acid comprising the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary thereto. In one aspect of this embodiment, the nucleic acid is recombinant.

Another embodiment of the present invention is a purified or isolated nucleic acid comprising at least 10 consecutive bases of the sequence of one of SEO ID NOs: 40-140 and 242-377 or one of the sequences complementary thereto. In one aspect of this embodiment, the nucleic acid comprises at least 15, 25, 30, 40, 50, 75, or 100 consecutive bases of one of the sequences of SEO ID NOs: 40-140 and 242-377 or one of the sequences complementary thereto. The nucleic acid may be a recombinant nucleic acid.

Another embodiment of the present invention is a purified or isolated nucleic acid of at least 15 bases capable of hybridizing under stringent conditions to the sequence of one of SEQ IO NOs: 40-140 and 242-377 or a sequence complementary to one of the sequences of SEQ ID NOs: 40-140 and 242-377. In one aspect of this embodiment, the nucleic acid is recombinant.

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Another embodiment of the present invention is a purified or isolated nucleic acid comprising the full coding sequences of one of SEQ ID NOs: 40-140 and 242-377, wherein the full coding sequence optionally comprises the sequence encoding signal peptide as well as the sequence encoding mature protein. In a preferred embodiment, the isolated or purified nucleic acid comprises the full coding sequence of one of SEQ ID Nos. 40, 42-44, 46, 48, 49, 51, 53, 60, 62-72, 76-78, 80-83, 85-88, 90, 93, 94, 97, 99-102, 104, 107-125, 127, 132, 135-138, 140 and 242-377 wherein the full coding sequence comprises the sequence encoding signal peptide and the sequence encoding mature protein. In one aspect of this embodiment, the nucleic acid is recombinant.

A further embodiment of the present invention is a purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40-140 and 242-377 which encode a mature protein. In a preferred embodiment, the purified or isolated nucleic acid comprises the nucleotides of one of SEQ ID NOs: 40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode a mature protein. In one aspect of this embodiment, the nucleic acid is recombinant.

Yet another embodiment of the present invention is a purified or isolated nucleic acid comprising the nucleotides of one of SEO ID NOs: 40-140 and 242-377 which encode the signal peptide. In a preferred embodiment, the purified or isolated nucleic acid comprises the nucleotides of SEO ID NOs: 40, 42-46, 48, 49, 51, 53, 57, 60, 62-73, 76-78, 80-83, 85-88, 90, 93-95, 97, 99-102, 104, 107-125, 127, 128, 130, 132, 134-140 and 242-377 which encode the signal peptide. In one aspect of this embodiment, the nucleic acid is recombinant.

Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of one of the sequences of SEQ ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of a mature protein included in one of the sequences of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the purified or isolated nucleic acid encodes a polypeptide having the sequence of a mature protein included in one of the sequences of SEQ ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.

Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of a signal peptide included in one of the sequences of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the purified or isolated nucleic acid encodes a polypeptide having the sequence of a signal peptide included in one of the sequences of SEQ ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.

Yet another embodiment of the present invention is a purified or isolated protein comprising the sequence of one of SEQ ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is a purified or isolated polypeptide comprising at least 10 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In one aspect of this embodiment, the purified or isolated polypeptide comprises at least 15, 20, 25, 35, 50, 75, 100, 150 or 200 consecutive

amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In still another aspect, the purified or isolated polypeptide comprises at least 25 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is an isolated or purified polypeptide comprising a signal peptide of one of the polypeptides of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the isolated or purified polypeptide comprises a signal peptide of one of the polypeptides of SEQ ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.

Yet another embodiment of the present invention is an isolated or purified polypeptide comprising a mature protein of one of the polypeptides of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the isolated or purified polypeptide comprises a mature protein of one of the polypeptides of SEQ ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.

A further embodiment of the present invention is a method of making a protein comprising one of the sequences of SEQ ID NO: 141-241 and 378-513, comprising the steps of obtaining a cDNA comprising one of the sequences of sequence of SEQ ID NO: 40-140 and 242-377, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the protein encoded by said cDNA. In one aspect of this embodiment, the method further comprises the step of isolating the protein.

Another embodiment of the present invention is a protein obtainable by the method described in the preceding paragraph.

Another embodiment of the present invention is a method of making a protein comprising the amino acid sequence of the mature protein contained in one of the sequences of SEQ ID NO: 141-241 and 378-513, comprising the steps of obtaining a cDNA comprising one of the nucleotides sequence of sequence of SEQ ID NO: 40-140 and 242-377 which encode for the mature protein, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the mature protein encoded by the cDNA. In one aspect of this embodiment, the method further comprises the step of isolating the protein.

Another embodiment of the present invention is a mature protein obtainable by the method described in the 30 preceding paragraph.

In a preferred embodiment, the above method comprises a method of making a protein comprising the amino acid sequence of the mature protein contained in one of the sequences of SEQ ID NO: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513, comprising the steps of obtaining a cDNA comprising one of the nucleotides sequence of sequence of SEQ ID NO:

40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode for the mature protein, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the mature protein encoded by the cDNA. In one aspect of this embodiment, the method further comprises the step of isolating the protein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary thereto described herein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids

comprising the full coding sequences of one of SEQ ID NDs: 4D-140 and 242-377, wherein the full coding sequence
comprises the sequence encoding signal peptide and the sequence encoding mature protein described herein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the nucleotides of one of SEQ ID NDs: 40-140 and 242-377 which encode a mature protein which are described herein. Preferably, the host cell contains the purified or isolated nucleic acids comprising the nucleotides of one of SEQ ID NOs: 40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode a mature protein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the nucleotides of one of SEQ ID NOs: 40·140 and 242·377 which encode the signal peptide which are described herein. Preferably, the host cell contains the purified or isolated nucleic acids comprising the nucleotides of one of SEQ ID Nos.: 40, 42·46, 48, 49, 51, 53, 57, 60, 62·73, 76·78, 80·83, 85·88, 90, 93·95, 97, 99·102, 104, 107·125, 127, 128, 130, 132, 134·140 and 242·377 which encode the signal peptide.

Another embodiment of the present invention is a purified or isolated antibody capable of specifically binding to a protein having the sequence of one of SEQ ID NOs: 141-241 and 378-513. In one aspect of this embodiment, the antibody is capable of binding to a polypeptide comprising at least 10 consecutive amino acids of the sequence of one of SEQ ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is an array of cDNAs or fragments thereof of at least 15 nucleotides in length which includes at least one of the sequences of SEQ ID NOs: 40-140 and 242-377, or one of the sequences complementary to the sequences of SEQ ID NOs: 40-140 and 242-377, or a fragment thereof of at least 15 consecutive nucleotides. In one aspect of this embodiment, the array includes at least two of the sequences of SEQ ID NOs: 40-140 and 242-377, or fragments thereof of at least 15 consecutive nucleotides. In another aspect of this embodiment, the array includes at least five of the sequences of SEQ ID NOs: 40-140 and 242-377, the sequences complementary to the sequences of SEQ ID NOs: 40-140 and 242-377, or fragments thereof of at least 15 consecutive nucleotides.

A further embodiment of the invention encompasses purified polynucleotides comprising an insert from a clone deposited in a deposit having an accession number selected from the group consisting of the accession numbers listed in Table VI or a fragment thereof comprising a contiguous span of at least 8, 10, 12, 15, 20, 25, 40, 60, 100, or 200 nucleotides of said insert. An additional embodiment of the invention encompasses purified polypeptides which comprise, consist of, or consist essentially of an amino acid sequence encoded by the insert from a clone deposited in a deposit having an accession number selected from the group consisting of the accession numbers listed in Table VI, as well as polypeptides which comprise a fragment of said amino acid sequence consisting of a signal peptide, a mature protein, or a contiguous span of at least 5, 8, 10, 12, 15, 20, 25, 40, 60, 100, or 200 amino acids encoded by said insert.

An additional embodiment of the invention encompasses purified polypeptides which comprise a contiguous span of at least 5, 8, 10, 12, 15, 20, 25, 40, 60, 100, or 200 amino acids of SEQ ID NOs: 158, 174, 175, 196, 226, 231, 232, wherein said contiguous span comprises at least one of the amino acid positions which was not shown to be identical to a public sequence in any of Figures 11 to 15. Also encompassed by the invention are purified polynuculeotides encoding said polypeptides.

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Brief Description of the Drawings

Figure 1 is a summary of a procedure for obtaining cDNAs which have been selected to include the 5' ends of the mRNAs from which they are derived.

Figure 2 is an analysis of the 43 amino terminal amino acids of all human SwissProt proteins to determine the frequency of false positives and false negatives using the techniques for signal peptide identification described herein.

Figure 3 shows the distribution of von Heijne scores for 5' ESTs in each of the categories described herein and the probability that these 5' ESTs encode a signal peptide.

Figure 4 shows the distribution of 5' ESTs in each category and the number of 5' ESTs in each category having a given minimum von Heijne's score.

Figure 5 shows the tissues from which the mRNAs corresponding to the 5' ESTs in each of the categories described herein were obtained.

Figure 6 illustrates a method for obtaining extended cDNAs.

Figure 7 is a map of pED6dpc2. pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SSt cDNAs are cloned between EcoRI and Notl. PED vectors are described in Kaufman et al. 30 (1991), NAR 19: 4485-4490.

Figure 8 provides a schematic description of the promoters isolated and the way they are assembled with the corresponding 5' tags.

Figure 9 describes the transcription factor binding sites present in each of these promoters.

Figure 10 is an alignment of the protein of SEQ ID NO: 217 with the human protein TFAR19 that may play a role in apoptosis (Genbank accession number AF014955, SEQ ID NO: 516).

Figure 11 is an alignment of the proteins of SEQ ID NOs: 174, 175 and 232 with a human secreted protein (Genseq accession number W36955, SEQ ID NO: 517).

Figure 12 is an alignment of the protein of SEQ ID NO: 231 with the human E25 protein (Genbank accession number AF038953, SEQ ID NO: 515).

Figure 13 is an alignment of the protein of SEQ ID NO: 196 with the human seventransmembrane protein (Genbank accession number Y11395, SEQ ID NO: 518).

Figure 14 is an alignment of the protein of SEQ ID NOs: 158 with the murine subunit 7a of the COP9 complex 10 (Genbank accession number AF071316, SEQ ID ND: 519).

Figure 15 is an alignment of the protein of SEQ ID NO: 226 with the bovine subunit B14.5B of the NADHubiquinone oxidureductase complex (Arizmendi *et al, FEBS Lett.*, **313** : 80-84 (1992) and Swissprot accession -number Q02827, SEQ ID NO: 514).

Detailed Description of the Preferred Embodiment

15 I. Obtaining 5' ESTs

The present extended cDNAs were obtained using 5' ESTs which were isolated as described below.

A. Chemical Methods for Obtaining mRNAs having Intact 5' Ends

In order to obtain the 5' ESTs used to obtain the extended cDNAs of the present invention, mRNAs having intact 5' ends must be obtained. Currently, there are two approaches for obtaining such mRNAs. One of these 20 approaches is a chemical modification method involving derivatization of the 5' ends of the mRNAs and selection of the derivatized mRNAs. The 5' ends of eucaryotic mRNAs possess a structure referred to as a "cap" which comprises a guanosine methylated at the 7 position. The cap is joined to the first transcribed base of the mRNA by a 5', 5'triphosphate bond. In some instances, the 5' guanosine is methylated in both the 2 and 7 positions. Rarely, the 5' guanosine is trimethylated at the 2, 7 and 7 positions. In the chemical method for obtaining mRNAs having intact 5' 25 ends, the 5' cap is specifically derivatized and coupled to a reactive group on an immobilizing substrate. This specific derivatization is based on the fact that only the ribose linked to the methylated guanosine at the 5' end of the mRNA and the ribose linked to the base at the 3' terminus of the mRNA, possess 2', 3'-cis diols. Optionally, where the 3' terminal ribose has a 2', 3'-cis diol, the 2', 3'-cis diol at the 3' end may be chemically modified, substituted, converted, or eliminated, leaving only the ribose linked to the methylated guanosine at the 5' end of the mRNA with a 2', 3'-cis diol. A 30 variety of techniques are available for eliminating the 2', 3'-cis diol on the 3' terminal ribose. For example, controlled alkaline hydrolysis may be used to generate mRNA fragments in which the 3' terminal ribose is a 3'-phosphate, 2'phosphate or (2', 3')-cyclophosphate. Thereafter, the fragment which includes the original 3' ribose may be eliminated from the mixture through chromatography on an oligo-dT column. Alternatively, a base which lacks the 2', 3'-cis diol

may be added to the 3' end of the mRNA using an RNA ligase such as T4 RNA ligase. Example 1 below describes a method for ligation of pCp to the 3' end of messenger RNA.

EXAMPLE 1

Ligation of the Nucleoside Diphosphate pCp to the 3' End of Messenger RNA

1 μg of RNA was incubated in a final reaction medium of 10 μl in the presence of 5 U of T_4 phage RNA ligase in the buffer provided by the manufacturer (Gibco · BRL), 40 U of the RNase inhibitor RNasin (Promega) and, 2 μl of 32 pCp (Amersham #PB 10208).

The incubation was performed at 37°C for 2 hours or overnight at 7-8°C.

Following modification or elimination of the 2', 3'-cis diol at the 3' ribose, the 2', 3'-cis diol present at the 5' end of the mRNA may be oxidized using reagents such as NaBH, NaBH, CN, or sodium periodate, thereby converting the 2', 3'-cis diol to a dialdehyde. Example 2 describes the oxidation of the 2', 3'-cis diol at the 5' end of the mRNA with sodium periodate.

EXAMPLE 2

Dxidation of 2', 3'-cis diol at the 5' End of the mRNA

0.1 DD unit of either a capped oligoribonucleotide of 47 nucleotides (including the cap) or an uncapped oligoribonucleotide of 46 nucleotides were treated as follows. The oligoribonucleotides were produced by in vitro transcription using the transcription kit "AmpliScribe T7" (Epicentre Technologies). As indicated below, the DNA template for the RNA transcript contained a single cytosine. To synthesize the uncapped RNA, all four NTPs were included in the in vitro transcription reaction. To obtain the capped RNA, GTP was replaced by an analogue of the cap, m7G(5')ppp(5')G. This compound, recognized by polymerase, was incorporated into the 5' end of the nascent transcript during the step of initiation of transcription but was not capable of incorporation during the extension step. Consequently, the resulting RNA contained a cap at its 5' end. The sequences of the oligoribonucleotides produced by the in vitro transcription reaction were:

+ Cap:

25 5'm7GpppGCAUCCUACUCCCAUCCAAUUCCACCCUAACUCCUCCCAUCUCCAC-3' (SEQ ID NO:1)

-Cap:

5'-pppGCAUCCUACUCCCAUCCAAUUCCACCCUAACUCCUCCCAUCUCCAC-3' (SEQ ID NO:2)

The oligoribonucleotides were dissolved in 9 µl of acetate buffer (0.1 M sodium acetate, pH 5.2) and 3 µl of freshly prepared 0.1 M sodium periodate solution. The mixture was incubated for 1 hour in the dark at 4°C or room temperature. Thereafter, the reaction was stopped by adding 4 µl of 10% ethylene glycol. The product was ethanol precipitated, resuspended in 10µl or more of water or appropriate buffer and dialyzed against water.

The resulting aldehyde groups may then be coupled to molecules having a reactive amine group, such as hydrazine, carbazide, thiocarbazide or semicarbazide groups, in order to facilitate enrichment of the 5' ends of the mRNAs. Molecules having reactive amine groups which are suitable for use in selecting mRNAs having intact 5' ends

include avidin, proteins, antibodies, vitamins, ligands capable of specifically binding to receptor molecules, or oligonucleotides. Example 3 below describes the coupling of the resulting dialdehyde to biotin.

EXAMPLE 3

Coupling of the Dialdehyde with Biotin

5 The oxidation product obtained in Example 2 was dissolved in 50 μl of sodium acetate at a pH of between 5 and 5.2 and 50 μl of freshly prepared 0.02 M solution of biotin hydrazide in a methoxyethanol/water mixture (1:1) of formula:

In the compound used in these experiments, n = 5. However, it will be appreciated that other commercially available hydrazides may also be used, such as molecules of the formula above in which n varies from 0 to 5.

The mixture was then incubated for 2 hours at 37°C. Following the incubation, the mixture was precipitated with ethanol and dialyzed against distilled water.

Example 4 demonstrates the specificity of the biotinylation reaction.

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EXAMPLE 4

Specificity of Biotinylation

The specificity of the biotinylation for capped mRNAs was evaluated by gel electrophoresis of the following samples:

Sample 1. The 46 nucleotide uncapped in vitro transcript prepared as in Example 2 and labeled with ³²pCp as described in Example 1.

Sample 2. The 46 nucleotide uncapped in vitro transcript prepared as in Example 2, labeled with ³²pCp as described in Example 1, treated with the oxidation reaction of Example 2, and subjected to the biotinylation conditions of Example 3.

Sample 3. The 47 nucleotide capped in vitro transcript prepared as in Example 2 and labeled with ³²pCp as described in Example 1.

Sample 4. The 47 nucleotide capped in vitro transcript prepared as in Example 2, labeled with ³²pCp as described in Example 1, treated with the oxidation reaction of Example 2, and subjected to the biotinylation conditions of Example 3.

Samples 1 and 2 had indentical migration rates, demonstrating that the uncapped RNAs were not oxidized and biotinylated. Sample 3 migrated more slowly than Samples 1 and 2, while Sample 4 exhibited the slowest migration.

The difference in migration of the RNAs in Samples 3 and 4 demonstrates that the capped RNAs were specifically biotinylated.

In some cases, mRNAs having intact 5' ends may be enriched by binding the molecule containing a reactive amine group to a suitable solid phase substrate such as the inside of the vessel containing the mRNAs, magnetic beads, 5 chromatography matrices, or nylon or nitrocellulose membranes. For example, where the molecule having a reactive amine group is biotin, the solid phase substrate may be coupled to avidin or streptavidin. Alternatively, where the molecule having the reactive amine group is an antibody or receptor ligand, the solid phase substrate may be coupled to the cognate antigen or receptor. Finally, where the molecule having a reactive amine group comprises an oligonucleotide, the solid phase substrate may comprise a complementary oligonucleotide.

The mRNAs having intact 5' ends may be released from the solid phase following the enrichment procedure. For example, where the dialdehyde is coupled to biotin hydrazide and the solid phase comprises streptavidin, the mRNAs may be released from the solid phase by simply heating to 95 degrees Celsius in 2% SDS. In some methods, the molecule having a reactive amine group may also be cleaved from the mRNAs having intact 5' ends following enrichment. Example 5 describes the capture of biotinylated mRNAs with streptavidin coated beads and the release of the 15 biotinylated mRNAs from the beads following enrichment.

EXAMPLE 5

Capture and Release of Biotinylated mRNAs Using Strepatividin Coated Beads

The streptavidin-coated magnetic beads were prepared according to the manufacturer's instructions (CPG Inc., USA). The biotinylated mRNAs were added to a hybridization buffer (1.5 M NaCl, pH 5 - 6). After incubating for 30 20 minutes, the unbound and nonbiotinylated material was removed. The beads were washed several times in water with 1% SDS. The beads obtained were incubated for 15 minutes at 95°C in water containing 2% SDS.

Example 6 demonstrates the efficiency with which biotinylated mRNAs were recovered from the streptavidin coated beads.

EXAMPLE 6

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Efficiency of Recovery of Biotinylated mRNAs

The efficiency of the recovery procedure was evaluated as follows. RNAs were labeled with 32pCp, oxidized, biotinylated and bound to streptavidin coated beads as described above. Subsequently, the bound RNAs were incubated for 5, 15 or 30 minutes at 95°C in the presence of 2% SDS.

The products of the reaction were analyzed by electrophoresis on 12% polyacrylamide gels under denaturing 30 conditions (7 M urea). The gels were subjected to autoradiography. During this manipulation, the hydrazone bonds were not reduced.

Increasing amounts of nucleic acids were recovered as incubation times in 2% SOS increased, demonstrating that biotinylated mRNAs were efficiently recovered.

In an alternative method for obtaining mRNAs having intact 5' ends, an oligonucleotide which has been derivatized to contain a reactive amine group is specifically coupled to mRNAs having an intact cap. Preferably, the 3' end of the mRNA is blocked prior to the step in which the aldehyde groups are joined to the derivatized oligonucleotide, as described above, so as to prevent the derivatized oligonucleotide from being joined to the 3' end of the mRNA. For example, pCp may be attached to the 3' end of the mRNA using T4 RNA ligase. However, as discussed above, blocking the 3' end of the mRNA is an optional step. Derivatized oligonucleotides may be prepared as described below in Example 7.

EXAMPLE 7

Derivatization of the Dligonucleotide

An oligonucleotide phosphorylated at its 3' end was converted to a 3' hydrazide in 3' by treatment with an aqueous solution of hydrazine or of dihydrazide of the formula H₂N(R1)NH₂ at about 1 to 3 M, and at pH 4.5, in the presence of a carbodiimide type agent soluble in water such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide at a final concentration of 0.3 M at a temperature of 8°C overnight.

The derivatized oligonucleotide was then separated from the other agents and products using a standard technique for isolating oligonucleotides.

As discussed above, the mRNAs to be enriched may be treated to eliminate the 3' DH groups which may be present thereon. This may be accomplished by enzymatic ligation of sequences lacking a 3' DH, such as pCp, as described above in Example 1. Alternatively, the 3' DH groups may be eliminated by alkaline hydrolysis as described in Example 8 below.

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EXAMPLE 8

Alkaline Hydrolysis of mRNA

The mRNAs may be treated with alkaline hydrolysis as follows. In a total volume of 100µl of 0.1N sodium hydroxide, 1.5µg mRNA is incubated for 40 to 60 minutes at 4°C. The solution is neutralized with acetic acid and precipitated with ethanol.

Following the optional elimination of the 3' DH groups, the diol groups at the 5' ends of the mRNAs are oxidized as described below in Example 9.

EXAMPLE 9

Oxidation of Diols

Up to 1 0D unit of RNA was dissolved in 9 µl of buffer (0.1 M sodium acetate, pH 6.7 or water) and 3 µl of freshly prepared 0.1 M sodium periodate solution. The reaction was incubated for 1 h in the dark at 4°C or room temperature. Following the incubation, the reaction was stopped by adding 4 µl of 10% ethylene glycol. Thereafter the mixture was incubated at room temperature for 15 minutes. After ethanol precipitation, the product was resuspended in 10µl or more of water or appropriate buffer and dialyzed against water.

Following oxidation of the diol groups at the 5' ends of the mRNAs, the derivatized oligonucleotide was joined to the resulting aldehydes as described in Example 10.

EXAMPLE 10

Reaction of Aldehydes with Derivatized Oligonucleotides

The oxidized mRNA was dissolved in an acidic medium such as 50 µl of sodium acetate pH 4-6. 50 µl of a solution of the derivatized oligonucleotide was added such that an mRNA:derivatized oligonucleotide ratio of 1:20 was obtained and mixture was reduced with a borohydride. The mixture was allowed to incubate for 2 h at 37°C or overnight (14 h) at 10°C. The mixture was ethanol precipitated, resuspended in 10µl or more of water or appropriate buffer and dialyzed against distilled water. If desired, the resulting product may be analyzed using acrylamide gel electrophoresis, HPLC analysis, or other conventional techniques.

Following the attachment of the derivatized oligonucleotide to the mRNAs, a reverse transcription reaction may be performed as described in Example 11 below.

EXAMPLE 11

Reverse Transcription of mRNAs

An oligodeoxyribonucleotide was derivatized as follows. 3 OD units of an oligodeoxyribonucleotide of sequence ATCAAGAATTCGCACGAGACCATTA (SEQ ID NO:3) having 5'-DH and 3'-P ends were dissolved in 70 µl of a 1.5 M hydroxybenzotriazole solution, pH 5.3, prepared in dimethylformamide/water (75:25) containing 2 µg of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide. The mixture was incubated for 2 h 30 min at 22°C. The mixture was then precipitated twice in LiClO₄/acetone. The pellet was resuspended in 200 µl of 0.25 M hydrazine and incubated at 8°C from 3 to 14 h. Following the hydrazine reaction, the mixture was precipitated twice in LiClO₄/acetone.

The messenger RNAs to be reverse transcribed were extracted from blocks of placenta having sides of 2 cm which had been stored at -80°C. The mRNA was extracted using conventional acidic phenol techniques. Oligo-dT chromatography was used to purify the mRNAs. The integrity of the mRNAs was checked by Northern-blotting.

The diol groups on 7 µg of the placental mRNAs were oxidized as described above in Example 9. The

derivatized oligonucleotide was joined to the mRNAs as described in Example 10 above except that the precipitation step was replaced by an exclusion chromatography step to remove derivatized oligodeoxyribonucleotides which were not joined to mRNAs. Exclusion chromatography was performed as follows:

10 ml of AcA34 (BioSepra#230151) gel were equilibrated in 50 ml of a solution of 10 mM Tris pH 8.0, 300 mM NaCl, 1 mM EDTA, and 0.05% SDS. The mixture was allowed to sediment. The supernatant was eliminated and \(\) 30 the gel was resuspended in 50 ml of buffer. This procedure was repeated 2 or 3 times.

A glass bead (diameter 3 mm) was introduced into a 2 ml disposable pipette (length 25 cm). The pipette was filled with the gel suspension until the height of the gel stabilized at 1 cm from the top of the pipette. The column was then equilibrated with 20 ml of equilibration buffer (10 mM Tris HCl pH 7.4, 20 mM NaCl).

10 μ l of the mRNA which had been reacted with the derivatized oligonucleotide were mixed in 39 μ l of 10 mM urea and 2 μ l of blue-glycerol buffer, which had been prepared by dissolving 5 mg of bromophenol blue in 60% glycerol (v/v), and passing the mixture through a filter with a filter of diameter 0.45 μ m.

The column was loaded. As soon as the sample had penetrated, equilibration buffer was added. 100 µl

fractions were collected. Derivatized oligonucleotide which had not been attached to mRNA appeared in fraction 16 and later fractions. Fractions 3 to 15 were combined and precipitated with ethanol.

The mRNAs which had been reacted with the derivatized oligonucleotide were spotted on a nylon membrane and hybridized to a radioactive probe using conventional techniques. The radioactive probe used in these hybridizations was an oligodeoxyribonucleotide of sequence TAATGGTCTCGTGCGAATTCTTGAT (SEQ ID NO:4) which was anticomplementary to the derivatized oligonucleotide and was labeled at its 5' end with 32P. 1/10th of the mRNAs which had been reacted with the derivatized oligonucleotide was spotted in two spots on the membrane and the membrane was visualized by autoradiography after hybridization of the probe. A signal was observed, indicating that the derivatized oligonucleotide had been joined to the mRNA.

The remaining 9/10 of the mRNAs which had been reacted with the derivatized oligonucleotide was reverse transcribed as follows. A reverse transcription reaction was carried out with reverse transcriptase following the manufacturer's instructions. To prime the reaction, 50 pmol of nonamers with random sequence were used.

A portion of the resulting cDNA was spotted on a positively charged nylon membrane using conventional methods. The cDNAs were spotted on the membrane after the cDNA:RNA heteroduplexes had been subjected to an alkaline hydrolysis in order to eliminate the RNAs. An oligonucleotide having a sequence identical to that of the derivatized oligonucleotide was labeled at its 5' end with ³²P and hybridized to the cDNA blots using conventional techniques. Single-stranded cDNAs resulting from the reverse transcription reaction were spotted on the membrane. As controls, the blot contained 1 pmol, 100 fmol, 50 fmol, 10 fmol and 1 fmol respectively of a control oligodeoxyribonucleotide of sequence identical to that of the derivatized oligonucleotide. The signal observed in the spots containing the cDNA indicated that approximately 15 fmol of the derivatized oligonucleotide had been reverse transcribed.

These results demonstrate that the reverse transcription can be performed through the cap and, in particular, that reverse transcriptase crosses the 5'-P-P-P-5' bond of the cap of eukaryotic messenger RNAs.

The single stranded cDNAs obtained after the above first strand synthesis were used as template for PCR reactions. Two types of reactions were carried out. First, specific amplification of the mRNAs for the alpha globin, dehydrogenase, pp15 and elongation factor E4 were carried out using the following pairs of oligodeoxyribonucleotide primers.

alpha-globin

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GLO-S: CCG ACA AGA CCA ACG TCA AGG CCG C (SEQ ID NO:5)

GLO-As: TCA CCA GCA GGC AGT GGC TTA GGA G 3' (SEQ ID NO:6)

dehydrogenase

3 DH-S: AGT GAT TCC TGC TAC TTT GGA TGG C (SEQ ID NO:7)

3 DH-As: GCT TGG TCT TGT TCT GGA GTT TAG A (SEQ ID NO:8)

pp15

PP15-S: TCC AGA ATG GGA GAC AAG CCA ATT T (SEQ ID NO:9)

5 PP15-As: AGG GAG GAG GAA ACA GCG TGA GTC C (SEQ ID ND:10)

Elongation factor E4

EFA1-S: ATG GGA AAG GAA AAG ACT CAT ATC A (SEQ ID NO:11)

EF1A-As: AGC AGC AAC AAT CAG GAC AGC ACA G (SEQ ID ND:12)

Non specific amplifications were also carried out with the antisense (_As) oligodeoxyribonucleotides of the pairs described above and a primer chosen from the sequence of the derivatized oligodeoxyribonucleotide (ATCAAGAATTCGCACGAGACCATTA) (SEQ ID ND:13).

A 1.5% agarose gel containing the following samples corresponding to the PCR products of reverse transcription was stained with ethidium bromide. (1/20th of the products of reverse transcription were used for each PCR reaction).

- Sample 1: The products of a PCR reaction using the globin primers of SEQ ID NDs 5 and 6 in the presence of cDNA.
 - Sample 2: The products of a PCR reaction using the globin primers of SEQ ID NOs 5 and 6 in the absence of added cDNA.
- Sample 3: The products of a PCR reaction using the dehydrogenase primers of SEQ ID NOs 7 and 8 in the 20 presence of cDNA.
 - Sample 4: The products of a PCR reaction using the dehydrogenase primers of SEQ ID NOs 7 and 8 in the absence of added cDNA.
 - Sample 5: The products of a PCR reaction using the pp15 primers of SEQ ID NDs 9 and 10 in the presence of cDNA.
- Sample 6: The products of a PCR reaction using the pp15 primers of SEQ ID NDs 9 and 10 in the absence of added cDNA.
 - Sample 7: The products of a PCR reaction using the EIE4 primers of SEQ ID NOs 11 and 12 in the presence of added cDNA.
- Sample 8: The products of a PCR reaction using the EIE4 primers of SEQ ID NOs 11 and 12 in the absence of 30 added cDNA.

In Samples 1, 3, 5 and 7, a band of the size expected for the PCR product was observed, indicating the presence of the corresponding sequence in the cDNA population.

PCR reactions were also carried out with the antisense oligonucleotides of the globin and dehydrogenase primers (SEQ ID NOs 6 and 8) and an oligonucleotide whose sequence corresponds to that of the derivatized

oligonucleotide. The presence of PCR products of the expected size in the samples corresponding to samples 1 and 3 above indicated that the derivatized oligonucleotide had been incorporated.

The above examples summarize the chemical procedure for enriching mRNAs for those having intact 5' ends.

Further detail regarding the chemical approaches for obtaining mRNAs having intact 5' ends are disclosed in

International Application No. W096/34981, published November 7, 1996.

Strategies based on the above chemical modifications to the 5' cap structure may be utilized to generate cDNAs which have been selected to include the 5' ends of the mRNAs from which they are derived. In one version of such procedures, the 5' ends of the mRNAs are modified as described above. Thereafter, a reverse transcription reaction is conducted to extend a primer complementary to the mRNA to the 5' end of the mRNA. Single stranded RNAs are eliminated to obtain a population of cDNA/mRNA heteroduplexes in which the mRNA includes an intact 5' end. The resulting heteroduplexes may be captured on a solid phase coated with a molecule capable of interacting with the molecule used to derivatize the 5' end of the mRNA. Thereafter, the strands of the heteroduplexes are separated to recover single stranded first cDNA strands which include the 5' end of the mRNA. Second strand cDNA synthesis may then proceed using conventional techniques. For example, the procedures disclosed in WO 96/34981 or in Carninci, P. et al. High-Efficiency Full-Length cDNA Cloning by Biotinylated CAP Trapper. Genomics 37:327-336 (1996) may be employed to select cDNAs which include the sequence derived from the 5' end of the coding sequence of the mRNA.

Following ligation of the oligonucleotide tag to the 5' cap of the mRNA, a reverse transcription reaction is conducted to extend a primer complementary to the mRNA to the 5' end of the mRNA. Following elimination of the RNA component of the resulting heteroduplex using standard techniques, second strand cDNA synthesis is conducted with a primer complementary to the oligonucleotide tag.

Figure 1 summarizes the above procedures for obtaining cDNAs which have been selected to include the 5' ends of the mRNAs from which they are derived.

B. Enzymatic Methods for Obtaining mRNAs having Intact 5' Ends

Dther techniques for selecting cDNAs extending to the 5' end of the mRNA from which they are derived are fully enzymatic. Some versions of these techniques are disclosed in Dumas Milne Edwards J.B. (Doctoral Thesis of Paris VI University, Le clonage des ADNc complets: difficultes et perspectives nouvelles. Apports pour l'etude de la regulation de l'expression de la tryptophane hydroxylase de rat, 20 Dec. 1993), EPO 625572 and Kato et al. Construction of a Human Full-Length cDNA Bank. Gene 150:243-250 (1994).

Briefly, in such approaches, isolated mRNA is treated with alkaline phosphatase to remove the phosphate groups present on the 5' ends of uncapped incomplete mRNAs. Following this procedure, the cap present on full length mRNAs is enzymatically removed with a decapping enzyme such as T4 polynucleotide kinase or tobacco acid pyrophosphatase. An oligonucleotide, which may be either a DNA oligonucleotide or a DNA-RNA hybrid oligonucleotide having RNA at its 3' end, is then ligated to the phosphate present at the 5' end of the decapped mRNA using T4 RNA

ligase. The oligonucleotide may include a restriction site to facilitate cloning of the cDNAs following their synthesis. Example 12 below describes one enzymatic method based on the doctoral thesis of Dumas.

EXAMPLE 12

Enzymatic Approach for Obtaining 5' ESTs

Twenty micrograms of PolyA + RNA were dephosphorylated using Calf Intestinal Phosphatase (Biolabs). After a phenol chloroform extraction, the cap structure of mRNA was hydrolysed using the Tobacco Acid Pyrophosphatase (purified as described by Shinshi et al., Biochemistry 15: 2185-2190, 1976) and a hemi 5'DNA/RNA-3' oligonucleotide having an unphosphorylated 5' end, a stretch of adenosine ribophosphate at the 3' end, and an EcoRI site near the 5' end was ligated to the 5'P ends of mRNA using the T4 RNA ligase (Biolabs). Dligonucleotides suitable for use in this procedure are preferably 30-50 bases in length. Oligonucleotides having an unphosphorylated 5' end may be synthesized by adding a fluorochrome at the 5' end. The inclusion of a stretch of adenosine ribophosphates at the 3' end of the oligonucleotide increases ligation eificiency. It will be appreciated that the oligonucleotide may contain cloning sites other than EcoRI.

Following ligation of the oligonucleotide to the phosphate present at the 5' end of the decapped mRNA, first
and second strand cDNA synthesis may be carried out using conventional methods or those specified in EPO 625,572
and Kato et al. Construction of a Human Full-Length cDNA Bank. Gene 150:243-250 (1994), and Dumas Milne Edwards,
supra. The resulting cDNA may then be ligated into vectors such as those disclosed in Kato et al. Construction of a
Human Full-Length cDNA Bank. Gene 150:243-250 (1994) or other nucleic acid vectors known to those skilled in the art
using techniques such as those described in Sambrook et al., Molecular Cloning: A Laboratory Manual 2d Ed., Cold
Spring Harbor Laboratory Press. 1989.

II. Characterization of 5' ESTs

The above chemical and enzymatic approaches for enriching mRNAs having intact 5' ends were employed to obtain 5' ESTs. First, mRNAs were prepared as described in Example 13 below.

EXAMPLE 13

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Preparation of mRNA

Total human RNAs or PolyA + RNAs derived from 29 different tissues were respectively purchased from LABIMO and CLDNTECH and used to generate 44 cDNA libraries as described below. The purchased RNA had been isolated from cells or tissues using acid guanidium thiocyanate-phenol-chloroform extraction (Chomczyniski, P and Sacchi, N., Analytical Biochemistry 162:156·159, 1987). PolyA + RNA was isolated from total RNA (LABIMD) by two passes of oligodT chromatography, as described by Aviv and Leder (Aviv, H. and Leder, P., Proc. Natl. Acad. Sci. USA 69:1408-1412, 1972) in order to eliminate ribosomal RNA.

The quality and the integrity of the poly A + were checked. Northern blots hybridized with a globin probe were used to confirm that the mRNAs were not degraded. Contamination of the PolyA + mRNAs by ribosomal sequences was checked using RNAs blots and a probe derived from the sequence of the 28S RNA. Preparations of mRNAs with less

than 5% of ribosomal RNAs were used in library construction. To avoid constructing libraries with RNAs contaminated by exogenous sequences (prokaryotic or fungal), the presence of bacterial 16S ribosomal sequences or of two highly expressed mRNAs was examined using PCR.

Following preparation of the mRNAs, the above described chemical and/or the enzymatic procedures for
enriching mRNAs having intact 5' ends discussed above were employed to obtain 5' ESTs from various tissues. In both
approaches an oligonucleotide tag was attached to the cap at the 5' ends of the mRNAs. The oligonucleotide tag had an
EcoRI site therein to facilitate later cloning procedures.

Following attachment of the oligonucleotide tag to the mRNA by either the chemical or enzymatic methods, the integrity of the mRNA was examined by performing a Northern blot with 200-500ng of mRNA using a probe complementary to the oligonucleotide tag.

EXAMPLE 14

cDNA Synthesis Using mRNA Templates Having Intact 5' Ends

For the mRNAs joined to oligonucleotide tags using both the chemical and enzymatic methods, first strand cDNA synthesis was performed using reverse transcriptase with random nonamers as primers. In order to protect

15 internal EcoRI sites in the cDNA from digestion at later steps in the procedure, methylated dCTP was used for first strand synthesis. After removal of RNA by an alkaline hydrolysis, the first strand of cDNA was precipitated using isopropanol in order to eliminate residual primers.

For both the chemical and the enzymatic methods, the second strand of the cDNA was synthesized with a Klenow fragment using a primer corresponding to the 5'end of the ligated oligonucleotide described in Example 12.

Preferably, the primer is 20-25 bases in length. Methylated dCTP was also used for second strand synthesis in order to protect internal EcoRI sites in the cDNA from digestion during the cloning process.

Following cDNA synthesis, the cDNAs were cloned into pBlueScript as described in Example 15 below.

EXAMPLE 15

Insertion of cDNAs into BlueScript

Following second strand synthesis, the ends of the cDNA were blunted with T4 DNA polymerase (Biolabs) and the cDNA was digested with EcoRI. Since methylated dCTP was used during cDNA synthesis, the EcoRI site present in the tag was the only site which was hemi-methylated. Consequently, only the EcoRI site in the oligonucleotide tag was susceptible to EcoRI digestion. The cDNA was then size fractionated using exclusion chromatography (AcA, Biosepra). Fractions corresponding to cDNAs of more than 150 bp were pooled and ethanol precipitated. The cDNA was directionally cloned into the Smal and EcoRI ends of the phagemid pBlueScript vector (Stratagene). The ligation mixture was electroporated into bacteria and propagated under appropriate antibiotic selection.

Clones containing the oligonucleotide tag attached were selected as described in Example 16 below.

EXAMPLE 16

Selection of Clones Having the Oligonucleotide Tag Attached Thereto

The plasmid DNAs containing 5' EST libraries made as described above were purified (Qiagen). A positive selection of the tagged clones was performed as follows. Briefly, in this selection procedure, the plasmid DNA was converted to single stranded DNA using gene II endonuclease of the phage F1 in combination with an exonuclease (Chang et al., Gene 127:95-8, 1993) such as exonuclease III or T7 gene 6 exonuclease. The resulting single stranded DNA was then purified using paramagnetic beads as described by Fry et al., Biotechniques, 13: 124-131, 1992. In this procedure, the single stranded DNA was hybridized with a biotinylated oligonucleotide having a sequence corresponding to the 3' end of the oligonucleotide described in Example 13. Preferably, the primer has a length of 20-25 bases. Clones including a sequence complementary to the biotinylated oligonucleotide were captured by incubation with streptavidin coated magnetic beads followed by magnetic selection. After capture of the positive clones, the plasmid DNA was released from the magnetic beads and converted into double stranded DNA using a DNA polymerase such as the ThermoSequenase obtained from Amersham Pharmacia Biotech. Alternatively, protocols such as the Gene Trapper kit (Gibco BRL) may be used. The double stranded DNA was then electroporated into bacteria. The percentage of positive clones having the 5' tag oligonucleotide was estimated to typically rank between 90 and 98% using dot blot analysis.

Following electroporation, the libraries were ordered in 384-microtiter plates (MTP). A copy of the MTP was stored for future needs. Then the libraries were transferred into 96 MTP and sequenced as described below.

EXAMPLE 17

Sequencing of Inserts in Selected Clones

Plasmid inserts were first amplified by PCR on PE 9600 thermocyclers (Perkin-Elmer), using standard SETA-A and SETA-B primers (Genset SA), AmpliTaqGold (Perkin-Elmer), dNTPs (Boehringer), buffer and cycling conditions as recommended by the Perkin-Elmer Corporation.

PCR products were then sequenced using automatic ABI Prism 377 sequencers (Perkin Elmer, Applied Biosystems Division, Foster City, CA). Sequencing reactions were performed using PE 9600 thermocyclers (Perkin Elmer) with standard dye-primer chemistry and ThermoSequenase (Amersham Life Science). The primers used were either T7 or 21M13 (available from Genset SA) as appropriate. The primers were labeled with the JOE, FAM, ROX and TAMRA dyes. The dNTPs and ddNTPs used in the sequencing reactions were purchased from Boehringer. Sequencing buffer, reagent concentrations and cycling conditions were as recommended by Amersham.

Following the sequencing reaction, the samples were precipitated with EtOH, resuspended in formamide loading buffer, and loaded on a standard 4% acrylamide gel. Electrophoresis was performed for 2.5 hours at 3000V on an ABI 377 sequencer, and the sequence data were collected and analyzed using the ABI Prism DNA Sequencing

Analysis Software, version 2.1.2.

The sequence data from the 44 cDNA libraries made as described above were transferred to a proprietary database, where quality control and validation steps were performed. A proprietary base-caller ("Trace"), working using a Unix system automatically flagged suspect peaks, taking into account the shape of the peaks, the inter-peak resolution, and the noise level. The proprietary base-caller also performed an automatic trimming. Any stretch of 25 or

fewer bases having more than 4 suspect peaks was considered unreliable and was discarded. Sequences corresponding to cloning vector or ligation oligonucleotides were automatically removed from the EST sequences. However, the resulting EST sequences may contain 1 to 5 bases belonging to the above mentioned sequences at their 5' end. If needed, these can easily be removed on a case by case basis.

5 Thereafter, the sequences were transferred to the proprietary NETGENE™ Database for further analysis as described below.

Following sequencing as described above, the sequences of the 5' ESTs were entered in a proprietary database called NETGENETM for storage and manipulation. It will be appreciated by those skilled in the art that the data could be stored and manipulated on any medium which can be read and accessed by a computer. Computer readable media include magnetically readable media, optically readable media, or electronically readable media. For example, the computer readable media may be a hard disc, a floppy disc, a magnetic tape, CD-ROM, RAM, or ROM as well as other types of other media known to those skilled in the art.

In addition, the sequence data may be stored and manipulated in a variety of data processor programs in a variety of formats. For example, the sequence data may be stored as text in a word processing file, such as

MicrosoftWORD or WORDPERFECT or as an ASCII file in a variety of database programs familiar to those of skill in the art, such as DB2, SYBASE, or DRACLE.

The computer readable media on which the sequence information is stored may be in a personal computer, a network, a server or other computer systems known to those skilled in the art. The computer or other system preferably includes the storage media described above, and a processor for accessing and manipulating the sequence data.

Once the sequence data has been stored it may be manipulated and searched to locate those stored sequences which contain a desired nucleic acid sequence or which encode a protein having a particular functional domain. For example, the stored sequence information may be compared to other known sequences to identify homologies, motifs implicated in biological function, or structural motifs.

Programs which may be used to search or compare the stored sequences include the MacPattern (EMBL),

25 BLAST, and BLAST2 program series (NCBI), basic local alignment search tool programs for nucleotide (BLASTN) and
peptide (BLASTX) comparisons (Altschul et al, J. Mol. Biol. 215: 403 (1990)) and FASTA (Pearson and Lipman, Proc.

Natl. Acad. Sci. USA, 85: 2444 (1988)). The BLAST programs then extend the alignments on the basis of defined
match and mismatch criteria.

Motifs which may be detected using the above programs include sequences encoding leucine zippers, helix-turn30 helix motifs, glycosylation sites, ubiquitination sites, alpha helices, and beta sheets, signal sequences encoding signal peptides which direct the secretion of the encoded proteins, sequences implicated in transcription regulation such as homeoboxes, acidic stretches, enzymatic active sites, substrate binding sites, and enzymatic cleavage sites.

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Before searching the cDNAs in the NETGENE™ database for sequence motifs of interest, cDNAs derived from mRNAs which were not of interest were identified and eliminated from further consideration as described in Example 18 below.

EXAMPLE 18

Elimination of Undesired Sequences from Further Consideration

5' ESTs in the NETGENETM database which were derived from undesired sequences such as transfer RNAs, ribosomal RNAs, mitochondrial RNAs, procaryotic RNAs, fungal RNAs, Alu sequences, L1 sequences, or repeat sequences were identified using the FASTA and BLASTN programs with the parameters listed in Table II.

To eliminate 5' ESTs encoding tRNAs from further consideration, the 5' EST sequences were compared to the sequences of 1190 known tRNAs obtained from EMBL release 38, of which 100 were human. The comparison was performed using FASTA on both strands of the 5' ESTs. Sequences having more than 80% homology over more than 60 nucleotides were identified as tRNAs. Of the 144,341 sequences screened, 26 were identified as tRNAs and eliminated from further consideration.

To eliminate 5' ESTs encoding rRNAs from further consideration, the 5' EST sequences were compared to the sequences of 2497 known rRNAs obtained from EMBL release 38, of which 73 were human. The comparison was performed using BLASTN on both strands of the 5' ESTs with the parameter S = 108. Sequences having more than 80% homology over stretches longer than 40 nucleotides were identified as rRNAs. Of the 144,341 sequences screened, 3,312 were identified as rRNAs and eliminated from further consideration.

To eliminate 5' ESTs encoding mtRNAs from further consideration, the 5' EST sequences were compared to the sequences of the two known mitochondrial genomes for which the entire genomic sequences are available and all sequences transcribed from these mitochondrial genomes including tRNAs, rRNAs, and mRNAs for a total of 38 sequences. The comparison was performed using BLASTN on both strands of the 5' ESTs with the parameter S = 108. Sequences having more than 80% homology over stretches longer than 40 nucleotides were identified as mtRNAs. Of the 144,341 sequences screened, 6,110 were identified as mtRNAs and eliminated from further consideration.

Sequences which might have resulted from exogenous contaminants were eliminated from further consideration by comparing the 5' EST sequences to release 46 of the EMBL bacterial and fungal divisions using BLASTN with the parameter S = 144. All sequences having more than 90% homology over at least 40 nucleotides were identified as exogenous contaminants. Of the 42 cDNA libraries examined, the average percentages of procaryotic and fungal sequences contained therein were 0.2% and 0.5% respectively. Among these sequences, only one could be identified as a sequence specific to fungi. The others were either fungal or procaryotic sequences having homologies with vertebrate sequences or including repeat sequences which had not been masked during the electronic comparison.

In addition, the 5' ESTs were compared to 6093 Alu sequences and 1115 L1 sequences to mask 5' ESTs containing such repeat sequences from further consideration. 5' ESTs including THE and MER repeats, SSTR sequences or satellite, micro-satellite, or telomeric repeats were also eliminated from further consideration. On average, 11.5% of

the sequences in the libraries contained repeat sequences. Of this 11.5%, 7% contained Alu repeats, 3.3% contained L1 repeats and the remaining 1.2% were derived from the other types of repetitive sequences which were screened. These percentages are consistent with those found in cDNA libraries prepared by other groups. For example, the cDNA libraries of Adams et al. contained between 0% and 7.4% Alu repeats depending on the source of the RNA which was used to prepare the cDNA library (Adams et al., *Nature* 377:174, 1996).

The sequences of those 5' ESTs remaining after the elimination of undesirable sequences were compared with the sequences of known human mRNAs to determine the accuracy of the sequencing procedures described above.

EXAMPLE 19

Measurement of Sequencing Accuracy by Comparison to Known Sequences

To further determine the accuracy of the sequencing procedure described above, the sequences of 5' ESTs derived from known sequences were identified and compared to the known sequences. First, a FASTA analysis with overhangs shorter than 5 bp on both ends was conducted on the 5' ESTs to identify those matching an entry in the public human mRNA database. The 6655 5' ESTs which matched a known human mRNA were then realigned with their cognate mRNA and dynamic programming was used to include substitutions, insertions, and deletions in the list of "errors" which would be recognized. Errors occurring in the last 10 bases of the 5' EST sequences were ignored to avoid the inclusion of spurious cloning sites in the analysis of sequencing accuracy.

This analysis revealed that the sequences incorporated in the NETGENETM database had an accuracy of more than 99.5%.

To determine the efficiency with which the above selection procedures select cDNAs which include the 5' ends of their corresponding mRNAs, the following analysis was performed.

EXAMPLE 20

Determination of Efficiency of 5' EST Selection

To determine the efficiency at which the above selection procedures isolated 5' ESTs which included sequences close to the 5' end of the mRNAs from which they were derived, the sequences of the ends of the 5' ESTs which were derived from the elongation factor 1 subunit α and ferritin heavy chain genes were compared to the known cDNA sequences for these genes. Since the transcription start sites for the elongation factor 1 subunit α and ferritin heavy chain are well characterized, they may be used to determine the percentage of 5' ESTs derived from these genes which included the authentic transcription start sites.

For both genes, more than 95% of the cDNAs included sequences close to or upstream of the 5' end of the 30 corresponding mRNAs.

To extend the analysis of the reliability of the procedures for isolating 5' ESTs from ESTs in the NETGENETM database, a similar analysis was conducted using a database composed of human mRNA sequences extracted from GenBank database release 97 for comparison. For those 5' ESTs derived from mRNAs included in the GeneBank database, more than 85% had their 5' ends close to the 5' ends of the known sequence. As some of the mRNA

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sequences available in the GenBank database are deduced from genomic sequences, a 5' end matching with these sequences will be counted as an internal match. Thus, the method used here underestimates the yield of ESTs including the authentic 5' ends of their corresponding mRNAs.

The EST libraries made above included multiple 5' ESTs derived from the same mRNA. The sequences of such 5' ESTs were compared to one another and the longest 5' ESTs for each mRNA were identified. Overlapping cDNAs were assembled into continuous sequences (contigs). The resulting continuous sequences were then compared to public databases to gauge their similarity to known sequences, as described in Example 21 below.

EXAMPLE 21

Clustering of the 5' ESTs and Calculation of Novelty Indices for cDNA Libraries

For each sequenced EST library, the sequences were clustered by the 5' end. Each sequence in the library was compared to the others with BLASTN2 (direct strand, parameters S = 107). ESTs with High Scoring Segment Pairs (HSPs) at least 25 bp long, having 95% identical bases and beginning closer than 10 bp from each EST 5' end were grouped. The longest sequence found in the cluster was used as representative of the cluster. A global clustering between libraries was then performed leading to the definition of super-contigs.

To assess the yield of new sequences within the EST libraries, a novelty rate (NR) was defined as: NR = 100 X (Number of new unique sequences found in the library/Total number of sequences from the library). Typically, novelty rating range between 10% and 41% depending on the tissue from which the EST library was obtained. For most of the libraries, the random sequencing of 5' EST libraries was pursued until the novelty rate reached 20%.

Following characterization as described above, the collection of 5' ESTs in NETGENETM was screened to 20 identify those 5' ESTs bearing potential signal sequences as described in Example 22 below.

EXAMPLE 22

Identification of Potential Signal Sequences in 5' ESTs

The 5' ESTs in the NETGENETM database were screened to identify those having an uninterrupted open reading frame (DRF) longer than 45 nucleotides beginning with an ATG codon and extending to the end of the EST.

25 Approximately half of the cDNA sequences in NETGENETM contained such an DRF. The DRFs of these 5' ESTs were searched to identify potential signal motifs using slight modifications of the procedures disclosed in Von Heijne, G. A New Method for Predicting Signal Sequence Cleavage Sites. Nucleic Acids Res. 14:4683-4690 (1986). Those 5' EST sequences encoding a 15 amino acid long stretch with a score of at least 3.5 in the Von Heijne signal peptide identification matrix were considered to possess a signal sequence. Those 5' ESTs which matched a known human mRNA or EST sequence and had a 5' end more than 20 nucleotides downstream of the known 5' end were excluded from further analysis. The remaining cDNAs having signal sequences therein were included in a database called SIGNALTAGTM.

To confirm the accuracy of the above method for identifying signal sequences, the analysis of Example 23 was performed.

EXAMPLE 23

Confirmation of Accuracy of Identification of Potential Signal Sequences in 5' ESTs

The accuracy of the above procedure for identifying signal sequences encoding signal peptides was evaluated by applying the method to the 43 amino terminal amino acids of all human SwissProt proteins. The computed Von Heijne score for each protein was compared with the known characterization of the protein as being a secreted protein or a non-secreted protein. In this manner, the number of non-secreted proteins having a score higher than 3.5 (false positives) and the number of secreted proteins having a score lower than 3.5 (false negatives) could be calculated.

Using the results of the above analysis, the probability that a peptide encoded by the 5' region of the mRNA is in fact a genuine signal peptide based on its Von Heijne's score was calculated based on either the assumption that 10% of human proteins are secreted or the assumption that 20% of human proteins are secreted. The results of this analysis are shown in Figures 2 and 3.

Using the above method of identifying secretory proteins, 5' ESTs for human glucagon, gamma interferon induced monokine precursor, secreted cyclophilin-like protein, human pleiotropin, and human biotinidase precursor all of which are polypeptides which are known to be secreted, were obtained. Thus, the above method successfully identified those 5' ESTs which encode a signal peptide.

To confirm that the signal peptide encoded by the 5' ESTs actually functions as a signal peptide, the signal sequences from the 5' ESTs may be cloned into a vector designed for the identification of signal peptides. Some signal peptide identification vectors are designed to confer the ability to grow in selective medium on host cells which have a signal sequence operably inserted into the vector. For example, to confirm that a 5' EST encodes a genuine signal peptide, the signal sequence of the 5' EST may be inserted upstream and in frame with a non-secreted form of the yeast invertase gene in signal peptide selection vectors such as those described in U.S. Patent No. 5,536,637. Growth of host cells containing signal sequence selection vectors having the signal sequence from the 5' EST inserted therein confirms that the 5' EST encodes a genuine signal peptide.

Alternatively, the presence of a signal peptide may be confirmed by cloning the extended cDNAs obtained using
the ESTs into expression vectors such as pXT1 (as described below), or by constructing promoter-signal sequencereporter gene vectors which encode fusion proteins between the signal peptide and an assayable reporter protein. After
introduction of these vectors into a suitable host cell, such as COS cells or NIH 3T3 cells, the growth medium may be
harvested and analyzed for the presence of the secreted protein. The medium from these cells is compared to the
medium from cells containing vectors lacking the signal sequence or extended cDNA insert to identify vectors which
encode a functional signal peptide or an authentic secreted protein.

Those 5' ESTs which encoded a signal peptide, as determined by the method of Example 22 above, were further grouped into four categories based on their homology to known sequences. The categorization of the 5' ESTs is described in Example 24 below.

Categorization of 5' ESTs Encoding a Signal Peptide

Those 5' ESTs having a sequence not matching any known vertebrate sequence nor any publicly available EST sequence were designated "new." Of the sequences in the SIGNALTAG™ database, 947 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category.

Those 5' ESTs having a sequence not matching any vertebrate sequence but matching a publicly known EST were designated "EST-ext", provided that the known EST sequence was extended by at least 40 nucleotides in the 5' direction. Of the sequences in the SIGNALTAGTM database, 150 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category.

Those ESTs not matching any vertebrate sequence but matching a publicly known EST without extending the known EST by at least 40 nucleotides in the 5' direction were designated "EST." Of the sequences in the SIGNALTAGTM database, 599 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category.

Those 5' ESTs matching a human mRNA sequence but extending the known sequence by at least 40 nucleotides in the 5' direction were designated "VERT-ext." Of the sequences in the SIGNALTAG™ database, 23 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category. Included in this category was a 5' EST which extended the known sequence of the human translocase mRNA by more than 200 bases in the 5' direction. A 5' EST which extended the sequence of a human tumor suppressor gene in the 5' direction was also identified.

Figure 4 shows the distribution of 5' ESTs in each category and the number of 5' ESTs in each category having a given minimum von Heijne's score.

Each of the 5' ESTs was categorized based on the tissue from which its corresponding mRNA was obtained, 20 as described below in Example 25.

EXAMPLE 25

Categorization of Expression Patterns

Figure 5 shows the tissues from which the mRNAs corresponding to the 5' ESTs in each of the above described categories were obtained.

In addition to categorizing the 5' ESTs by the tissue from which the cDNA library in which they were first identified was obtained, the spatial and temporal expression patterns of the mRNAs corresponding to the 5' ESTs, as well as their expression levels, may be determined as described in Example 26 below. Characterization of the spatial and temporal expression patterns and expression levels of these mRNAs is useful for constructing expression vectors capable of producing a desired level of gene product in a desired spatial or temporal manner, as will be discussed in more detail.

30 below.

In addition, 5' ESTs whose corresponding mRNAs are associated with disease states may also be identified. For example, a particular disease may result from lack of expression, over expression, or under expression of an mRNA corresponding to a 5' EST. By comparing mRNA expression patterns and quantities in samples taken from healthy

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individuals with those from individuals suffering from a particular disease, 5' ESTs responsible for the disease may be identified.

It will be appreciated that the results of the above characterization procedures for 5' ESTs also apply to extended cDNAs (obtainable as described below) which contain sequences adjacent to the 5' ESTs. It will also be appreciated that if it is desired to defer characterization until extended cDNAs have been obtained rather than characterizing the ESTs themselves, the above characterization procedures can be applied to characterize the extended cDNAs after their isolation.

EXAMPLE 26

Evaluation of Expression Levels and Patterns of mRNAs

10 <u>Corresponding to 5' ESTs or Extended cDNAs</u>

Expression levels and patterns of mRNAs corresponding to 5' ESTs or extended cDNAs (obtainable as described below) may be analyzed by solution hybridization with long probes as described in International Patent Application No. WO 97/05277. Briefly, a 5' EST, extended cDNA, or fragment thereof corresponding to the gene encoding the mRNA to be characterized is inserted at a cloning site immediately downstream of a bacteriophage (T3, T7 or SP6) RNA polymerase promoter to produce antisense RNA. Preferably, the 5' EST or extended cDNA has 100 or more nucleotides. The plasmid is linearized and transcribed in the presence of ribonucleotides comprising modified ribonucleotides (i.e. biotin-UTP and DIG-UTP). An excess of this doubly labeled RNA is hybridized in solution with mRNA isolated from cells or tissues of interest. The hybridizations are performed under standard stringent conditions (40-50°C for 16 hours in an 80% formamide, 0.4 M NaCl buffer, pH 7-8). The unhybridized probe is removed by digestion with ribonucleases specific for single-stranded RNA (i.e. RNases CL3, T1, Phy M, U2 or A). The presence of the biotin-UTP modification enables capture of the hybrid on a microtitration plate coated with streptavidin. The presence of the DIG modification enables the hybrid to be detected and quantified by ELISA using an anti-DIG antibody coupled to alkaline phosphatase.

The 5' ESTs, extended cDNAs, or fragments thereof may also be tagged with nucleotide sequences for the
serial analysis of gene expression (SAGE) as disclosed in UK Patent Application No. 2 305 241 A. In this method,
cDNAs are prepared from a cell, tissue, organism or other source of nucleic acid for which it is desired to determine gene
expression patterns. The resulting cDNAs are separated into two pools. The cDNAs in each pool are cleaved with a first
restriction endonuclease, called an "anchoring enzyme," having a recognition site which is likely to be present at least
once in most cDNAs. The fragments which contain the 5' or 3' most region of the cleaved cDNA are isolated by binding
to a capture medium such as streptavidin coated beads. A first oligonucleotide linker having a first sequence for
hybridization of an amplification primer and an internal restriction site for a "tagging endonuclease" is ligated to the
digested cDNAs in the first pool. Digestion with the second endonuclease produces short "tag" fragments from the
cDNAs.

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A second oligonucleotide having a second sequence for hybridization of an amplification primer and an internal restriction site is ligated to the digested cDNAs in the second pool. The cDNA fragments in the second pool are also digested with the "tagging endonuclease" to generate short "tag" fragments derived from the cDNAs in the second pool. The "tags" resulting from digestion of the first and second pools with the anchoring enzyme and the tagging 5 endonuclease are ligated to one another to produce "ditags." In some embodiments, the ditags are concatamerized to produce ligation products containing from 2 to 200 ditags. The tag sequences are then determined and compared to the sequences of the 5' ESTs or extended cDNAs to determine which 5' ESTs or extended cDNAs are expressed in the cell, tissue, organism, or other source of nucleic acids from which the tags were derived. In this way, the expression pattern of the 5' ESTs or extended cDNAs in the cell, tissue, organism, or other source of nucleic acids is obtained.

Quantitative analysis of gene expression may also be performed using arrays. As used herein, the term array means a one dimensional, two dimensional, or multidimensional arrangement of full length cDNAs (i.e. extended cDNAs which include the coding sequence for the signal peptide, the coding sequence for the mature protein, and a stop codon), extended cDNAs, 5' ESTs or fragments of the full length cDNAs, extended cDNAs, or 5' ESTs of sufficient length to permit specific detection of gene expression. Preferably, the fragments are at least 15 nucleotides in length. More 15 preferably, the fragments are at least 100 nucleotides in length. More preferably, the fragments are more than 100 nucleotides in length. In some embodiments the fragments may be more than 500 nucleotides in length.

For example, quantitative analysis of gene expression may be performed with full length cDNAs, extended cDNAs, 5' ESTs, or fragments thereof in a complementary DNA microarray as described by Schena et al. (Science 270:467-470, 1995; Proc. Natl. Acad. Sci. U.S.A. 93:10614-10619, 1996). Full length cDNAs, extended cDNAs, 5' 20 ESTs or fragments thereof are amplified by PCR and arrayed from 96-well microtiter plates onto silylated microscope slides using high-speed robotics. Printed arrays are incubated in a humid chamber to allow rehydration of the array elements and rinsed, once in 0.2% SDS for 1 min, twice in water for 1 min and once for 5 min in sodium borohydride solution. The arrays are submerged in water for 2 min at 95°C, transferred into 0.2% SDS for 1 min, rinsed twice with water, air dried and stored in the dark at 25°C.

Cell or tissue mRNA is isolated or commercially obtained and probes are prepared by a single round of reverse transcription. Probes are hybridized to 1 cm² microarrays under a 14 x 14 mm glass coverslip for 6-12 hours at 60°C. Arrays are washed for 5 min at 25°C in low stringency wash buffer (1 x SSC/0.2% SDS), then for 10 min at room temperature in high stringency wash buffer (0.1 x SSC/0.2% SDS). Arrays are scanned in 0.1 x SSC using a fluorescence laser scanning device fitted with a custom filter set. Accurate differential expression measurements are obtained by taking the average of the ratios of two independent hybridizations.

Quantitative analysis of the expression of genes may also be performed with full length cDNAs, extended cDNAs, 5' ESTs, or fragments thereof in complementary DNA arrays as described by Pietu et al. (Genome Research 6:492-503, 1996). The full length cDNAs, extended cDNAs, 5' ESTs or fragments thereof are PCR amplified and spotted on membranes. Then, mRNAs originating from various tissues or cells are labeled with radioactive nucleotides. WO 99/31236 PCT/IB98/02122

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After hybridization and washing in controlled conditions, the hybridized mRNAs are detected by phospho-imaging or autoradiography. Duplicate experiments are performed and a quantitative analysis of differentially expressed mRNAs is then performed.

Alternatively, expression analysis of the 5' ESTs or extended cDNAs can be done through high density

nucleotide arrays as described by Lockhart et al. (Nature Biotechnology 14: 1675-1680, 1996) and Sosnowsky et al.

(Proc. Natl. Acad. Sci. 94:1119-1123, 1997). Oligonucleotides of 15-50 nucleotides corresponding to sequences of the 5' ESTs or extended cDNAs are synthesized directly on the chip (Lockhart et al., supra) or synthesized and then addressed to the chip (Sosnowski et al., supra). Preferably, the oligonucleotides are about 20 nucleotides in length.

cDNA probes labeled with an appropriate compound, such as biotin, digoxigenin or fluorescent dye, are

synthesized from the appropriate mRNA population and then randomly fragmented to an average size of 50 to 100 nucleotides. The said probes are then hybridized to the chip. After washing as described in Lockhart et al., supra and application of different electric fields (Sosnowsky et al., Proc. Natl. Acad. Sci. 94:1119-1123)., the dyes or labeling compounds are detected and quantified. Duplicate hybridizations are performed. Comparative analysis of the intensity of the signal originating from cDNA probes on the same target oligonucleotide in different cDNA samples indicates a differential expression of the mRNA corresponding to the 5' EST or extended cDNA from which the oligonucleotide sequence has been designed.

III. Use of 5' ESTs to Clone Extended cDNAs and to Clone the Corresponding Genomic DNAs

Once 5' ESTs which include the 5' end of the corresponding mRNAs have been selected using the procedures described above, they can be utilized to isolate extended cDNAs which contain sequences adjacent to the 5' ESTs. The extended cDNAs may include the entire coding sequence of the protein encoded by the corresponding mRNA, including the authentic translation start site, the signal sequence, and the sequence encoding the mature protein remaining after cleavage of the signal peptide. Such extended cDNAs are referred to herein as "full length cDNAs." Alternatively, the extended cDNAs may include only the sequence encoding the mature protein remaining after cleavage of the signal peptide, or only the sequence encoding the signal peptide.

Example 27 below describes a general method for obtaining extended cDNAs. Example 28 below describes the cloning and sequencing of several extended cDNAs, including extended cDNAs which include the entire coding sequence and authentic 5' end of the corresponding mRNA for several secreted proteins.

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The methods of Examples 27, 28, and 29 can also be used to obtain extended cDNAs which encode less than the entire coding sequence of the secreted proteins encoded by the genes corresponding to the 5' ESTs. In some embodiments, the extended cDNAs isolated using these methods encode at least 10 amino acids of one of the proteins encoded by the sequences of SEQ ID NOs: 40-140 and 242-377. In further embodiments, the extended cDNAs encode at least 20 amino acids of the proteins encoded by the sequences of SEQ ID NOs: 40-140 and 242-377. In further embodiments, the extended cDNAs encode at least 30 amino acids of the sequences of SEQ ID NOs: 40-140 and

242-377. In a preferred embodiment, the extended cDNAs encode a full length protein sequence, which includes the protein coding sequences of SEQ ID NOs: 40-140 and 242-377.

EXAMPLE 27

General Method for Using 5' ESTs to Clone and Sequence Extended cDNAs

The following general method has been used to quickly and efficiently isolate extended cDNAs including sequence adjacent to the sequences of the 5' ESTs used to obtain them. This method may be applied to obtain extended cDNAs for any 5' EST in the NETGENETM database, including those 5' ESTs encoding secreted proteins. The method is summarized in Figure 6.

1. Obtaining Extended cDNAs

10 a) First strand synthesis

The method takes advantage of the known 5' sequence of the mRNA. A reverse transcription reaction is conducted on purified mRNA with a poly 14dT primer containing a 49 nucleotide sequence at its 5' end allowing the addition of a known sequence at the end of the cDNA which corresponds to the 3' end of the mRNA. For example, the primer may have the following sequence: 5'-ATC GTT GAG ACT CGT ACC AGC AGA GTC ACG AGA GAG ACT ACA CGG TAC TGG TTT TTT TTT TTT TTVN -3' (SEQ ID NO:14). Those skilled in the art will appreciate that other sequences may also be added to the poly dT sequence and used to prime the first strand synthesis. Using this primer and a reverse transcriptase such as the Superscript II (Gibco BRL) or Rnase H Minus M-MLV (Promega) enzyme, a reverse transcript anchored at the 3' polyA site of the RNAs is generated.

After removal of the mRNA hybridized to the first cDNA strand by alkaline hydrolysis, the products of the
alkaline hydrolysis and the residual poly dT primer are eliminated with an exclusion column such as an AcA34 (Biosepra)
matrix as explained in Example 11.

b) Second strand synthesis

A pair of nested primers on each end is designed based on the known 5' sequence from the 5' EST and the known 3' end added by the poly dT primer used in the first strand synthesis. Software used to design primers are either based on GC content and melting temperatures of oligonucleotides, such as OSP (Illier and Green, *PCR Meth. Appl.* 1:124-128, 1991), or based on the octamer frequency disparity method (Griffais et al., *Nucleic Acids Res.* 19: 3887-3891, 1991 such as PC-Rare (http://bioinformatics.weizmann.ac.il/software/PC-Rare/doc/manuel.html).

Preferably, the nested primers at the 5' end are separated from one another by four to nine bases. The 5' primer sequences may be selected to have melting temperatures and specificities suitable for use in PCR.

Preferably, the nested primers at the 3' end are separated from one another by four to nine bases. For example, the nested 3' primers may have the following sequences: (5'- CCA GCA GAG TCA CGA GAG AGA CTA CAC GG -3' (SEQ ID NO:15), and 5'- CAC GAG AGA GAC TAC ACG GTA CTG G -3' (SEQ ID NO:16). These primers were selected because they have melting temperatures and specificities compatible with their use in PCR. However, those skilled in the art will appreciate that other sequences may also be used as primers.

The first PCR run of 25 cycles is performed using the Advantage Tth Polymerase Mix (Clontech) and the outer primer from each of the nested pairs. A second 20 cycle PCR using the same enzyme and the inner primer from each of the nested pairs is then performed on 1/2500 of the first PCR product. Thereafter, the primers and nucleotides are removed.

5 2. Sequencing of Full Length Extended cDNAs or Fragments Thereof

Due to the lack of position constraints on the design of 5' nested primers compatible for PCR use using the OSP software, amplicons of two types are obtained. Preferably, the second 5' primer is located upstream of the translation initiation codon thus yielding a nested PCR product containing the whole coding sequence. Such a full length extended cDNA undergoes a direct cloning procedure as described in section a below. However, in some cases, the second 5' primer is located downstream of the translation initiation codon, thereby yielding a PCR product containing only part of the ORF. Such incomplete PCR products are submitted to a modified procedure described in section b below.

a) Nested PCR products containing complete ORFs

When the resulting nested PCR product contains the complete coding sequence, as predicted from the 5'EST sequence, it is cloned in an appropriate vector such as pED6dpc2, as described in section 3.

b) Nested PCR products containing incomplete ORFs

When the amplicon does not contain the complete coding sequence, intermediate steps are necessary to obtain both the complete coding sequence and a PCR product containing the full coding sequence. The complete coding sequence can be assembled from several partial sequences determined directly from different PCR products as described in the following section.

Once the full coding sequence has been completely determined, new primers compatible for PCR use are designed to obtain amplicons containing the whole coding region. However, in such cases, 3' primers compatible for PCR use are located inside the 3' UTR of the corresponding mRNA, thus yielding amplicons which lack part of this region, i.e. the polyA tract and sometimes the polyadenylation signal, as illustrated in figure 6. Such full length extended cDNAs are then cloned into an appropriate vector as described in section 3.

c) Sequencing extended cDNAs

Sequencing of extended cDNAs is performed using a Die Terminator approach with the AmpliTaq DNA polymerase FS kit available from Perkin Elmer.

In order to sequence PCR fragments, primer walking is performed using software such as OSP to choose

primers and automated computer software such as ASMG (Sutton et al., *Genome Science Technol.* 1: 9-19, 1995) to

construct contigs of walking sequences including the initial 5' tag using minimum overlaps of 32 nucleotides. Preferably, primer walking is performed until the sequences of full length cDNAs are obtained.

Completion of the sequencing of a given extended cDNA fragment is assessed as follows. Since sequences located after a polyA tract are difficult to determine precisely in the case of uncloned products, sequencing and primer

walking processes for PCR products are interrupted when a polyA tract is identified in extended cDNAs obtained as described in case b. The sequence length is compared to the size of the nested PCR product obtained as described above. Due to the limited accuracy of the determination of the PCR product size by gel electrophoresis, a sequence is considered complete if the size of the obtained sequence is at least 70 % the size of the first nested PCR product. If the 5 length of the sequence determined from the computer analysis is not at least 70% of the length of the nested PCR product, these PCR products are cloned and the sequence of the insertion is determined. When Northern blot data are available, the size of the mRNA detected for a given PCR product is used to finally assess that the sequence is complete. Sequences which do not fulfill the above criteria are discarded and will undergo a new isolation procedure.

Sequence data of all extended cDNAs are then transferred to a proprietary database, where quality controls 10 and validation steps are carried out as described in example 15.

3. Cloning of Full Length Extended cDNAs

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The PCR product containing the full coding sequence is then cloned in an appropriate vector. For example, the extended cDNAs can be cloned into the expression vector pED6dpc2 (DiscoverEase, Genetics Institute, Cambridge, MA) as follows. The structure of pED6dpc2 is shown in Figure 7. pED6dpc2 vector DNA is prepared with blunt ends by 15 performing an EcoRl digestion followed by a fill in reaction. The blunt ended vector is dephosphorylated. After removal of PCR primers and ethanol precipitation, the PCR product containing the full coding sequence or the extended cDNA obtained as described above is phosphorylated with a kinase subsequently removed by phenol-Sevag extraction and precipitation. The double stranded extended cDNA is then ligated to the vector and the resulting expression plasmid introduced into appropriate host cells.

Since the PCR products obtained as described above are blunt ended molecules that can be cloned in either direction, the orientation of several clones for each PCR product is determined. Then, 4 to 10 clones are ordered in microtiter plates and subjected to a PCR reaction using a first primer located in the vector close to the cloning site and a second primer located in the portion of the extended cDNA corresponding to the 3' end of the mRNA. This second primer may be the antisense primer used in anchored PCR in the case of direct cloning (case a) or the antisense primer located 25 inside the 3'UTR in the case of indirect cloning (case b). Clones in which the start codon of the extended cDNA is operably linked to the promoter in the vector so as to permit expression of the protein encoded by the extended cDNA are conserved and sequenced. In addition to the ends of cDNA inserts, approximately 50 bp of vector DNA on each side of the cDNA insert are also sequenced.

The cloned PCR products are then entirely sequenced according to the aforementioned procedure. In this case, contig assembly of long fragments is then performed on walking sequences that have already contigated for uncloned PCR products during primer walking. Sequencing of cloned amplicons is complete when the resulting contigs include the whole coding region as well as overlapping sequences with vector DNA on both ends.

4. Computer Analysis of Full Length Extended cDNA

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Sequences of all full length extended cDNAs are then submitted to further analysis as described below and using the parameters found in Table II with the following modifications. For screening of miscellaneous subdivisions of Genbank, FASTA was used instead of BLASTN and 15 nucleotide of homology was the limit instead of 17. For Alu detection, BLASTN was used with the following parameters: S = 72; identity = 70%; and length = 40 nucleotides.

- 5 Polyadenylation signal and polyA tail which were not search for the 5' ESTs were searched. For polyadenylation signal detection the signal (AATAAA) was searched with one permissible mismatch in the last ten nucleotides preceding the 5' end of the polyA. For the polyA, a stretch of 8 amino acids in the last 20 nucleotides of the sequence was searched with BLAST2N in the sense strand with the following parameters (W = 6, S = 10, E = 1000, and identity = 90%). Finally, patented sequences and ORF homologies were searched using, respectively, BLASTN and BLASTP on GenSEΩ
- 10 (Derwent's database of patented nucleotide sequences) and SWISSPROT for ORFs with the following parameters (W=8 and B=10). Before examining the extended full length cDNAs for sequences of interest, extended cDNAs which are not of interest are searched as follows.

a) Elimination of undesired sequences

Although 5'ESTs were checked to remove contaminant sequences as described in Example 18, a last verification was carried out to identify extended cDNAs sequences derived from undesired sequences such as vector RNAs, transfer RNAs, ribosomal rRNAs, mitochondrial RNAs, prokaryotic RNAs and fungal RNAs using the FASTA and BLASTN programs on both strands of extended cDNAs as described below.

To identify the extended cDNAs encoding vector RNAs, extended cDNAs are compared to the known sequences of vector RNA using the FASTA program. Sequences of extended cDNAs with more than 90% homology over stretches of 15 nucleotides are identified as vector RNA.

To identify the extended cDNAs encoding tRNAs, extended cDNA sequences were compared to the sequences of 1190 known tRNAs obtained from EMBL release 38, of which 100 were human. Sequences of extended cDNAs having more than 80% homology over 60 nucleotides using FASTA were identified as tRNA.

To identify the extended cDNAs encoding rRNAs, extended cDNA sequences were compared to the sequences
of 2497 known rRNAs obtained from EMBL release 38, of which 73 were human. Sequences of extended cDNAs having
more than 80% homology over stretches longer than 40 nucleotides using BLASTN were identified as rRNAs.

To identify the extended cDNAs encoding mtRNAs, extended cDNA sequences were compared to the sequences of the two known mitochondrial genomes for which the entire genomic sequences are available and all sequences transcribed from these mitochondrial genomes including tRNAs, rRNAs, and mRNAs for a total of 38 sequences. Sequences of extended cDNAs having more than 80% homology over stretches longer than 40 nucleotides using BLASTN were identified as mtRNAs.

Sequences which might have resulted from other exogenous contaminants were identified by comparing extended cDNA sequences to release 105 of Genbank bacterial and fungal divisions. Sequences of extended cDNAs

having more than 90% homology over 40 nucleotides using BLASTN were identified as exogenous prokaryotic or fungalcontaminants.

In addition, extended cDNAs were searched for different repeat sequences, including Alu sequences, L1 sequences, THE and MER repeats, SSTR sequences or satellite, micro-satellite, or telomeric repeats. Sequences of extended cDNAs with more than 70% homology over 40 nucleotide stretches using BLASTN were identified as repeat sequences and masked in further identification procedures. In addition, clones showing extensive homology to repeats, i.e., matches of either more than 50 nucleotides if the homology was at least 75% or more than 40 nucleotides if the homology was at least 90%, were flagged.

b) Identification of structural features

Structural features, e.g. polyA tail and polyadenylation signal, of the sequences of full length extended cDNAs are subsequently determined as follows.

A polyA tail is defined as a homopolymeric stretch of at least 11 A with at most one alternative base within it.

The polyA tail search is restricted to the last 20 nt of the sequence and limited to stretches of 11 consecutive A's because sequencing reactions are often not readable after such a polyA stretch. Stretches with 100% homology over 6 nucleotides are identified as polyA tails.

To search for a polyadenylation signal, the polyA tail is clipped from the full-length sequence. The 50 bp preceding the polyA tail are searched for the canonic polyadenylation AAUAAA signal allowing one mismatch to account for possible sequencing errors and known variation in the canonical sequence of the polyadenylation signal.

c) Identification of functional features

Functional features, e.g. ORFs and signal sequences, of the sequences of full length extended cDNAs were subsequently determined as follows.

The 3 upper strand frames of extended cDNAs are searched for ORFs defined as the maximum length fragments beginning with a translation initiation codon and ending with a stop codon. ORFs encoding at least 20 amino acids are preferred.

Each found ORF is then scanned for the presence of a signal peptide in the first 50 amino-acids or, where appropriate, within shorter regions down to 20 amino acids or less in the ORF, using the matrix method of von Heijne (Nuc. Acids Res. 14: 4683-4690 (1986)) and the modification described in Example 22.

d) Homology to either nucleotidic or proteic sequences

Sequences of full length extended cDNAs are then compared to known sequences on a nucleotidic or proteic 30 basis.

Sequences of full length extended cDNAs are compared to the following known nucleic acid sequences: vertebrate sequences (Genbank), EST sequences (Genbank), patented sequences (Geneseqn) and recently identified sequences (Genbank daily releases) available at the time of filing for the priority documents. Full length cONA sequences are also compared to the sequences of a private database (Genset internal sequences) in order to find sequences that

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have already been identified by applicants. Sequences of full length extended cDNAs with more than 90% homology over 30 nucleotides using either BLASTN or BLAST2N as indicated in Table III are identified as sequences that have already been described. Matching vertebrate sequences are subsequently examined using FASTA; full length extended cDNAs with more than 70% homology over 30 nucleotides are identified as sequences that have already been described.

ORFs encoded by full length extended cDNAs as defined in section c) are subsequently compared to known amino acid sequences found in Swissprot release CHP, PIR release PIR# and Genpept release GPEPT public databases using BLASTP with the parameter W = 8 and allowing a maximum of 10 matches. Sequences of full length extended cDNAs showing extensive homology to known protein sequences are recognized as already identified proteins.

In addition, the three-frame conceptual translation products of the top strand of full length extended cDNAs

10 are compared to publicly known amino acid sequences of Swissprot using BLASTX with the parameter E=0.001.

Sequences of full length extended cDNAs with more than 70% homology over 30 amino acid stretches are detected as already identified proteins.

5. Selection of Cloned Full Length Sequences of the Present Invention

Cloned full length extended cDNA sequences that have already been characterized by the aforementioned computer analysis are then submitted to an automatic procedure in order to preselect full length extended cDNAs containing sequences of interest.

a) Automatic sequence preselection

All complete cloned full length extended cDNAs clipped for vector on both ends are considered. First, a negative selection is operated in order to eliminate unwanted cloned sequences resulting from either contaminants or PCR artifacts as follows. Sequences matching contaminant sequences such as vector RNA, tRNA, mtRNA, rRNA sequences are discarded as well as those encoding ORF sequences exhibiting extensive homology to repeats as defined in section 4 a). Sequences obtained by direct cloning using nested primers on 5' and 3' tags (section 1. case a) but lacking polyA tail are discarded. Only ORFs containing a signal peptide and ending either before the polyA tail (case a) or before the end of the cloned 3'UTR (case b) are kept. Then, ORFs containing unlikely mature proteins such as mature proteins which size is less than 20 amino acids or less than 25% of the immature protein size are eliminated.

In the selection of the OFR, priority was given to the ORF and the frame corresponding to the polypeptides described in SignalTag Patents (United States Patent Application Serial Nos: 08/905,223; 08/905,135; 08/905,051; 08/905,144; 08/905,279; 08/904,468; 08/905,134; and 08/905,133). If the ORF was not found among the OFRs described in the SignalTag Patents, the ORF encoding the signal peptide with the highest score according to Von Heijne method as defined in Example 22 was chosen. If the scores were identical, then the longest ORF was chosen.

Sequences of full length extended cDNA clones are then compared pairwise with BLAST after masking of the repeat sequences. Sequences containing at least 90% homology over 30 nucleotides are clustered in the same class. Each cluster is then subjected to a cluster analysis that detects sequences resulting from internal priming or from

alternative splicing, identical sequences or sequences with several frameshifts. This automatic analysis serves as a basis for manual selection of the sequences.

b) Manual sequence selection

Manual selection is carried out using automatically generated reports for each sequenced full length extended cDNA clone. During this manual procedures, a selection is operated between clones belonging to the same class as follows. ORF sequences encoded by clones belonging to the same class are aligned and compared. If the homology between nucleotidic sequences of clones belonging to the same class is more than 90% over 30 nucleotide stretches or if the homology between amino acid sequences of clones belonging to the same class is more than 80% over 20 amino acid stretches, than the clones are considered as being identical. The chosen ORF is the best one according to the criteria mentioned below. If the nucleotide and amino acid homologies are less than 90% and 80% respectively, the clones are said to encode distinct proteins which can be both selected if they contain sequences of interest.

Selection of full length extended cD.NA clones encoding sequences of interest is performed using the following criteria. Structural parameters (initial tag, polyadenylation site and signal) are first checked. Then, homologies with known nucleic acids and proteins are examined in order to determine whether the clone sequence match a known nucleic/proteic sequence and, in the latter case, its covering rate and the date at which the sequence became public. If there is no extensive match with sequences other than ESTs or genomic DNA, or if the clone sequence brings substantial new information, such as encoding a protein resulting from alternative slicing of an mRNA coding for an already known protein, the sequence is kept. Examples of such cloned full length extended cDNAs containing sequences of interest are described in Example 28. Sequences resulting from chimera or double inserts as assessed by homology to other sequences are discarded during this procedure.

EXAMPLE 28

Cloning and Sequencing of Extended cDNAs

The procedure described in Example 27 above was used to obtain the extended cDNAs of the present invention. Using this approach, the full length cDNA of SEQ ID NO:17 was obtained. This cDNA falls into the "EST-ext" category described above and encodes the signal peptide MKKVLLLITAILAVAVG (SEQ ID NO: 18) having a von Heijne score of 8.2.

The full length cDNA of SEQ ID NO:19 was also obtained using this procedure. This cDNA falls into the "EST-ext" category described above and encodes the signal peptide MWWFQQGLSFLPSALVIWTSA (SEQ ID NO:20) having a von Heijne score of 5.5.

Another full length cDNA obtained using the procedure described above has the sequence of SEQ ID NO:21.

This cDNA, falls into the "EST-ext" category described above and encodes the signal peptide

MVLTTLPSANSANSPVNMPTTGPNSLSYASSALSPCLT (SEQ ID NO:22) having a von Heijne score of 5.9.

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The above procedure was also used to obtain a full length cDNA having the sequence of SEQ ID NO:23. This cDNA falls into the "EST-ext" category described above and encodes the signal peptide ILSTVTALTFAXA (SEQ ID NO:24) having a von Heijne score of 5.5.

The full length cDNA of SEQ ID NO:25 was also obtained using this procedure. This cDNA falls into the "new" category described above and encodes a signal peptide LVLTLCTLPLAVA (SEQ ID NO:26) having a von Heijne score of 10.1.

The full length cDNA of SEQ ID NO:27 was also obtained using this procedure. This cDNA falls into the "new" category described above and encodes a signal peptide LWLLFFLVTAIHA (SEQ ID NO:28) having a von Heijne score of 10.7.

The above procedures were also used to obtain the extended cDNAs of the present invention. 5' ESTs expressed in a variety of tissues were obtained as described above. The appended sequence listing provides the tissues from which the extended cDNAs were obtained. It will be appreciated that the extended cDNAs may also be expressed in tissues other than the tissue listed in the sequence listing.

5' ESTs obtained as described above were used to obtain extended cDNAs having the sequences of SEQ ID

NOs: 40·140 and 242·377. Table IV provides the sequence identification numbers of the extended cDNAs of the present invention, the locations of the full coding sequences in SEQ ID NOs: 40·140 and 242·377 (i.e. the nucleotides encoding both the signal peptide and the mature protein, listed under the heading FCS location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40·140 and 242·377 which encode the signal peptides (listed under the heading SigPep Location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40·140 and 242·377 which encode the mature proteins generated by cleavage of the signal peptides (listed under the heading Mature Polypeptide Location in Table IV), the locations in SEQ ID NOs: 40·140 and 242·377 of stop codons (listed under the heading Stop Codon Location in Table IV), the locations in SEQ ID NOs: 40·140 and 242·377 of polyA signals (listed under the heading Poly A Signal Location in Table IV) and the locations of polyA sites (listed under the heading Poly A Site Location in Table IV).

The polypeptides encoded by the extended cDNAs were screened for the presence of known structural or

functional motifs or for the presence of signatures, small amino acid sequences which are well conserved amongst the
members of a protein family. The conserved regions have been used to derive consensus patterns or matrices included in
the PROSITE data bank, in particular in the file prosite.dat (Release 13.0 of November 1995, located at
http://expasy.hcuge.ch/sprot/prosite.html. Prosite_convert and prosite_scan programs
(http://ulrec3.unil.ch/ftpserveur/prosite_scan) were used to find signatures on the extended cDNAs.

For each pattern obtained with the prosite_convert program from the prosite.dat file, the accuracy of the detection on a new protein sequence has been tested by evaluating the frequency of irrelevant hits on the population of human secreted proteins included in the data bank SWISSPROT. The ratio between the number of hits on shuffled proteins (with a window size of 20 amino acids) and the number of hits on native (unshuffled) proteins was used as an index. Every pattern for which the ration was greater than 20% (one hit on shuffled proteins for 5 hits on native

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proteins) was skipped during the search with prosite_scan. The program used to shuffle protein sequences (db_shuffled) and the program used to determine the statistics for each pattern in the protein data banks (prosite_statistics) are available on the ftp site http://ulrec3.unil.ch/ftpserveur/prosite_scan.

Table V lists the sequence identification numbers of the polypeptides of SEO IO NOs: 141-241 and 378-513, the locations of the amino acid residues of SEO ID NOs: 141-241 and 378-513 in the full length polypeptide (second column), the locations of the amino acid residues of SEO ID NOs: 141-241 and 378-513 in the signal peptides (third column), and the locations of the amino acid residues of SEO ID NOs: 141-241 and 378-513 in the mature polypeptide created by cleaving the signal peptide from the full length polypeptide (fourth column).

The nucleotide sequences of the sequences of SEQ ID NOs: 40·140 and 242·377 and the amino acid sequences

10 encoded by SEQ ID NOs: 40·140 and 242·377 (i.e. amino acid sequences of SEQ ID NOs: 141·241 and 378·513) are
provided in the appended sequence listing. In some instances, the sequences are preliminary and may include some
incorrect or ambiguous sequences or amino acids. The sequences of SEQ ID NOs: 40·140 and 242·377 can readily be
screened for any errors therein and any sequence ambiguities can be resolved by resequencing a fragment containing
such errors or ambiguities on both strands. Nucleic acid fragments for resolving sequencing errors or ambiguities may be
obtained from the deposited clones or can be isolated using the techniques described herein. Resolution of any such
ambiguities or errors may be facilitated by using primers which hybridize to sequences located close to the ambiguous or
erroneous sequences. For example, the primers may hybridize to sequences within 50·75 bases of the ambiguity or
error. Upon resolution of an error or ambiguity, the corresponding corrections can be made in the protein sequences
encoded by the DNA containing the error or ambiguity. For example, in the sequences of the present invention, ambiguities
in the sequence of SEQ ID NO: 131 were resolved. The amino acid sequence of the protein encoded by a particular clone
can also be determined by expression of the clone in a suitable host cell, collecting the protein, and determining its
sequence.

For each amino acid sequence, Applicants have identified what they have determined to be the reading frame best identifiable with sequence information available at the time of filing. Some of the amino acid sequences may

contain "Xaa" designators. These "Xaa" designators indicate either (1) a residue which cannot be identified because of
nucleotide sequence ambiguity or (2) a stop codon in the determined sequence where Applicants believe one should not
exist (if the sequence were determined more accurately).

Cells containing the extended cDNAs (SEQ ID NOs: 40-140 and 242-377) of the present invention in the vector pED6dpc2, are maintained in permanent deposit by the inventors at Genset, S.A., 24 Rue Royale, 75008 Paris, France.

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Pools of cells containing the extended cDNAs (SEQ ID NOs: 40-140 and 242-377), from which cells containing a particular polynucleotide are obtainable, were deposited with the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209 or the European Collection of Cell Cultures, Vaccine Research and Production Laboratory, Public Health Laboratory Service, Centre for Applied Microbiology and Research, Porton Down, Salisbury, Wiltshire SP4 OJG, United Kingdom. Each extended cDNA clone has been transfected into separate bacterial cells (E-

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coli) for this composite deposit. Table VI lists the deposit numbers of the clones containing the extended cDNAs of the present invention. Table VII provides the internal designation number assigned to each SEQ ID NO and indicates whether the sequence is a nucleic acid sequence or a protein sequence.

Each extended cDNA can be removed from the pED6dpc2 vector in which it was deposited by performing a 5 Notl, Pstl double digestion to produce the appropriate fragment for each clone. The proteins encoded by the extended cDNAs may also be expressed from the promoter in pED6dpc2.

Bacterial cells containing a particular clone can be obtained from the composite deposit as follows:

An oligonucleotide probe or probes should be designed to the sequence that is known for that particular clone. This sequence can be derived from the sequences provided herein, or from a combination of those sequences. The design 10 of the oligonucleotide probe should preferably follow these parameters:

- (a) It should be designed to an area of the sequence which has the fewest ambiguous bases ("N's"), if any;
- (b) Preferably, the probe is designed to have a Tm of approx. 80°C (assuming 2 degrees for each A or T and 4 degrees for each G or C). However, probes having melting temperatures between 40 °C and 80 °C may also be used provided that specificity is not lost.

The oligonucleotide should preferably be labeled with (-[32P]ATP (specific activity 6000 Ci/mmole) and T4 polynucleotide kinase using commonly employed techniques for labeling oligonucleotides. Other labeling techniques can also be used. Unincorporated label should preferably be removed by gel filtration chromatography or other established methods. The amount of radioactivity incorporated into the probe should be quantified by measurement in a scintillation counter. Preferably, specific activity of the resulting probe should be approximately 4X10⁶ dpm/pmole.

The bacterial culture containing the pool of full-length clones should preferably be thawed and 100 μ l of the stock used to inoculate a sterile culture flask containing 25 ml of sterile L-broth containing ampicillin at 100 ug/ml. The culture should preferably be grown to saturation at 37°C, and the saturated culture should preferably be diluted in fresh L-broth. Aliquots of these dilutions should preferably be plated to determine the dilution and volume which will yield approximately 5000 distinct and well-separated colonies on solid bacteriological media containing L-broth containing 25 ampicillin at 100 μg/ml and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other known methods of obtaining distinct, well-separated colonies can also be employed.

Standard colony hybridization procedures should then be used to transfer the colonies to nitrocellulose filters and lyse, denature and bake them.

The filter is then preferably incubated at 65°C for 1 hour with gentle agitation in 6X SSC (20X stock is 30 175.3 g NaC1/liter, 88.2 g Na citrate/liter, adjusted to pH 7.0 with NaOH) containing 0.5% SDS, 100 pg/ml of yeast RNA, and 10 mM EDTA (approximately 10 mL per 150 mm filter). Preferably, the probe is then added to the hybridization mix at a concentration greater than or equal to 1X106 dpm/mL. The filter is then preferably incubated at 65°C with gentle agitation overnight. The filter is then preferably washed in 500 mL of 2X SSC/0.1% SDS at room temperature with gentle shaking for 15 minutes. A third wash with 0.1X SSC/0.5% SDS at 65°C for 30 minutes to

1 hour is optional. The filter is then preferably dried and subjected to autoradiography for sufficient time to visualize the positives on the X-ray film. Other known hybridization methods can also be employed.

The positive colonies are picked, grown in culture, and plasmid DNA isolated using standard procedures. The clones can then be verified by restriction analysis, hybridization analysis, or DNA sequencing.

The plasmid DNA obtained using these procedures may then be manipulated using standard cloning techniques familiar to those skilled in the art. Alternatively, a PCR can be done with primers designed at both ends of the extended cDNA insertion. For example, a PCR reaction may be conducted using a primer having the sequence GGCCATACACTTGAGTGAC (SEQ ID NO:38) and a primer having the sequence ATATAGACAAACGCACACC (SEQ. ID. NO:39). The PCR product which corresponds to the extended cDNA can then be manipulated using standard cloning 10 techniques familiar to those skilled in the art.

In addition to PCR based methods for obtaining extended cDNAs, traditional hybridization based methods may also be employed. These methods may also be used to obtain the genomic DNAs which encode the mRNAs from which the 5' ESTs were derived, mRNAs corresponding to the extended cDNAs, or nucleic acids which are homologous to extended cDNAs or 5' ESTs. Example 29 below provides an example of such methods.

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EXAMPLE 29

Methods for Obtaining Extended cDNAs or Nucleic Acids Homologous to Extended cDNAs or 5' ESTs

A full length cDNA library can be made using the strategies described in Examples 13, 14, 15, and 16 above by replacing the random nonamer used in Example 14 with an oligo dT primer. For instance, the oligonucleotide of SEQ ID 20 NO:14 may be used.

Alternatively, a cDNA library or genomic DNA library may be obtained from a commercial source or made using techniques familiar to those skilled in the art. The library includes cDNAs which are derived from the mRNA corresponding to a 5' EST or which have homology to an extended cDNA or 5' EST. The cDNA library or genomic DNA library is hybridized to a detectable probe comprising at least 10 consecutive nucleotides from the 5' EST or extended 25 cDNA using conventional techniques. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST or extended cDNA. More preferably, the probe comprises at least 20-30 consecutive nucleotides from the 5' EST or extended cDNA. In some embodiments, the probe comprises at least 30 nucleotides from the 5' EST or extended cDNA. In other embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the 5' EST or extended cDNA.

Techniques for identifying cDNA clones in a cDNA library which hybridize to a given probe sequence are disclosed in Sambrook et al., Molecular Cloning: A Laboratory Manual 2d Ed., Cold Spring Harbor Laboratory Press, 1989. The same techniques may be used to isolate genomic DNAs.

Briefly, cDNA or genomic DNA clones which hybridize to the detectable probe are identified and isolated for further manipulation as follows. A probe comprising at least 10 consecutive nucleotides from the 5' EST or extended cDNA is labeled with a detectable label such as a radioisotope or a fluorescent molecule. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST or extended cDNA. More preferably, the probe comprises 20-30 consecutive nucleotides from the 5' EST or extended cDNA. In some embodiments, the probe comprises more than 30 nucleotides from the 5' EST or extended cDNA. In some embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the 5' EST or extended cDNA.

Techniques for labeling the probe are well known and include phosphorylation with polynucleotide kinase, nick translation, in vitro transcription, and non-radioactive techniques. The cDNAs or genomic DNAs in the library are transferred to a nitrocellulose or nylon filter and denatured. After incubation of the filter with a blocking solution, the filter is contacted with the labeled probe and incubated for a sufficient amount of time for the probe to hybridize to cDNAs or genomic DNAs containing a sequence capable of hybridizing to the probe.

By varying the stringency of the hybridization conditions used to identify extended cDNAs or genomic DNAs which hybridize to the detectable probe, extended cDNAS having different levels of homology to the probe can be identified and isolated. To identify extended cDNAs or genomic DNAs having a high degree of homology to the probe sequence, the melting temperature of the probe may be calculated using the following formulas:

For probes between 14 and 70 nucleotides in length the melting temperature (Tm) is calculated using the formula: Tm=81.5+16.6(log [Na+])+0.41(fraction G+C)-(600/N) where N is the length of the probe.

If the hybridization is carried out in a solution containing formamide, the melting temperature may be calculated using the equation Tm = 81.5 + 16.6(log [Na +]) + 0.41(fraction G + C) - (0.63% formamide) - (600/N) where N is the length of the probe.

Prehybridization may be carried out in 6X SSC, 5X Denhardt's reagent, 0.5% SDS, 100μg denatured fragmented salmon sperm DNA or 6X SSC, 5X Denhardt's reagent, 0.5% SDS, 100μg denatured fragmented salmon sperm DNA, 50% formamide. The formulas for SSC and Denhardt's solutions are listed in Sambrook et al., supra.

Hybridization is conducted by adding the detectable probe to the prehybridization solutions listed above. Where
the probe comprises double stranded DNA, it is denatured before addition to the hybridization solution. The filter is
contacted with the hybridization solution for a sufficient period of time to allow the probe to hybridize to extended
cDNAs or genomic DNAs containing sequences complementary thereto or homologous thereto. For probes over 200
nucleotides in length, the hybridization may be carried out at 15-25°C below the Tm. For shorter probes, such as
oligonucleotide probes, the hybridization may be conducted at 15-25°C below the Tm. Preferably, for hybridizations in

6X SSC, the hybridization is conducted at approximately 68°C. Preferably, for hybridizations in 50% formamide
containing solutions, the hybridization is conducted at approximately 42°C.

All of the foregoing hybridizations would be considered to be under "stringent" conditions. Following hybridization, the filter is washed in 2X SSC, 0.1% SDS at room temperature for 15 minutes. The filter is then washed

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with 0.1X SSC, 0.5% SDS at room temperature for 30 minutes to 1 hour. Thereafter, the solution is washed at the hybridization temperature in 0.1X SSC, 0.5% SDS. A final wash is conducted in 0.1X SSC at room temperature.

Extended cDNAs, nucleic acids homologous to extended cDNAs or 5' ESTs, or genomic DNAs which have hybridized to the probe are identified by autoradiography or other conventional techniques.

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The above procedure may be modified to identify extended cDNAs, nucleic acids homologous to extended cDNAs, or genomic DNAs having decreasing levels of homology to the probe sequence. For example, to obtain extended cDNAs, nucleic acids homologous to extended cDNAs, or genomic DNAs of decreasing homology to the detectable probe, less stringent conditions may be used. For example, the hybridization temperature may be decreased in increments of 5°C from 68°C to 42°C in a hybridization buffer having a Na + concentration of approximately 1M. Following 10 hybridization, the filter may be washed with 2X SSC, 0.5% SDS at the temperature of hybridization. These conditions are considered to be "moderate" conditions above 50°C and "low" conditions below 50°C.

Alternatively, the hybridization may be carried out in buffers, such as 6X SSC, containing formamide at a temperature of 42°C. In this case, the concentration of formamide in the hybridization buffer may be reduced in 5% increments from 50% to 0% to identify clones having decreasing levels of homology to the probe. Following 15 hybridization, the filter may be washed with 6X SSC, 0.5% SDS at 50°C. These conditions are considered to be "moderate" conditions above 25% formamide and "low" conditions below 25% formamide.

Extended cDNAs, nucleic acids homologous to extended cDNAs, or genomic DNAs which have hybridized to the probe are identified by autoradiography.

If it is desired to obtain nucleic acids homologous to extended cDNAs, such as allelic variants thereof or nucleic 20 acids encoding proteins related to the proteins encoded by the extended cDNAs, the level of homology between the hybridized nucleic acid and the extended cDNA or 5' EST used as the probe may readily be determined. To determine the level of homology between the hybridized nucleic acid and the extended cDNA or 5'EST from which the probe was derived, the nucleotide sequences of the hybridized nucleic acid and the extended cDNA or 5'EST from which the probe was derived are compared. For example, using the above methods, nucleic acids having at least 95% nucleic acid 25 homology to the extended cDNA or 5'EST from which the probe was derived may be obtained and identified. Similarly, by using progressively less stringent hybridization conditions one can obtain and identify nucleic acids having at least 90%, at least 85%, at least 80% or at least 75% homology to the extended cDNA or 5'EST from which the probe was derived. The level of homology between the hybridized nucleic acid and the extended cDNA or 5' EST used as the probe may be further determined using BLAST2N; parameters may be adapted depending on the sequence length and degree of 30 homology studied. In such comparisons, the default parameters or the parameters listed in Tables II and III may be used.

To determine whether a clone encodes a protein having a given amount of homology to the protein encoded by the extended cDNA or 5' EST, the amino acid sequence encoded by the extended cDNA or 5' EST is compared to the amino acid sequence encoded by the hybridizing nucleic acid. Homology is determined to exist when an amino acid sequence in the extended cDNA or 5' EST is closely related to an amino acid sequence in the hybridizing nucleic acid. A

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sequence is closely related when it is identical to that of the extended cDNA or 5' EST or when it contains one or more amino acid substitutions therein in which amino acids having similar characteristics have been substituted for one another. Using the above methods, one can obtain nucleic acids encoding proteins having at least 95%, at least 90%, at least 85%, at least 80% or at least 75% homology to the proteins encoded by the extended cDNA or 5'EST from which the probe was derived. Using the above methods and algorithms such as FASTA with parameters depending on the sequence length and degree of homology studied the level of homology may be determined. In determining the level of homology using FASTA, the default parameters or the parameters listed in Tables II or III may be used.

Alternatively, extended cDNAs may be prepared by obtaining mRNA from the tissue, cell, or organism of interest using mRNA preparation procedures utilizing poly A selection procedures or other techniques known to those skilled in the art. A first primer capable of hybridizing to the poly A tail of the mRNA is hybridized to the mRNA and a reverse transcription reaction is performed to generate a first cDNA strand.

The first cDNA strand is hybridized to a second primer containing at least 10 consecutive nucleotides of the sequences of the 5' EST for which an extended cDNA is desired. Preferably, the primer comprises at least 12, 15, or 17 consecutive nucleotides from the sequences of the 5' EST. More preferably, the primer comprises 20-30 consecutive nucleotides from the sequences of the 5' EST. In some embodiments, the primer comprises more than 30 nucleotides from the sequences of the 5' EST. If it is desired to obtain extended cDNAs containing the full protein coding sequence, including the authentic translation initiation site, the second primer used contains sequences located upstream of the translation initiation site. The second primer is extended to generate a second cDNA strand complementary to the first cDNA strand. Alternatively, RTPCR may be performed as described above using primers from both ends of the cDNA to be obtained.

Extended cDNAs containing 5' fragments of the mRNA may be prepared by contacting an mRNA comprising the sequence of the 5' EST for which an extended cDNA is desired with a primer comprising at least 10 consecutive nucleotides of the sequences complementary to the 5' EST, hybridizing the primer to the mRNAs, and reverse transcribing the hybridized primer to make a first cDNA strand from the mRNAs. Preferably, the primer comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST. More preferably, the primer comprises 20-30 consecutive nucleotides from the 5' EST.

Thereafter, a second cDNA strand complementary to the first cDNA strand is synthesized. The second cDNA strand may be made by hybridizing a primer complementary to sequences in the first cDNA strand to the first cDNA strand and extending the primer to generate the second cDNA strand.

The double stranded extended cDNAs made using the methods described above are isolated and cloned. The extended cDNAs may be cloned into vectors such as plasmids or viral vectors capable of replicating in an appropriate host cell. For example, the host cell may be a bacterial, mammalian, avian, or insect cell.

Techniques for isolating mRNA, reverse transcribing a primer hybridized to mRNA to generate a first cDNA strand, extending a primer to make a second cDNA strand complementary to the first cDNA strand, isolating the double

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stranded cDNA and cloning the double stranded cDNA are well known to those skilled in the art and are described in Current Protocols in Molecular Biology, John Wiley 503 Sons, Inc. 1997 and Sambrook et al. Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press, 1989.

Alternatively, kits for obtaining full length cDNAs, such as the GeneTrapper (Cat. No. 10356-020, Gibco, BRL),

may be used for obtaining full length cDNAs or extended cDNAs. In this approach, full length or extended cDNAs are
prepared from mRNA and cloned into double stranded phagemids. The cDNA library in the double stranded phagemids is
then rendered single stranded by treatment with an endonuclease, such as the Gene II product of the phage F1, and
Exonuclease III as described in the manual accompanying the GeneTrapper kit. A biotinylated oligonucleotide comprising
the sequence of a 5' EST, or a fragment containing at least 10 nucleotides thereof, is hybridized to the single stranded
phagemids. Preferably, the fragment comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST. More
preferably, the fragment comprises 20-30 consecutive nucleotides from the 5' EST. In some procedures, the fragment
may comprise more than 30 consecutive nucleotides from the 5' EST. For example, the fragment may comprises at least
40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the 5' EST.

Hybrids between the biotinylated oligonucleotide and phagemids having inserts containing the 5' EST sequence are isolated by incubating the hybrids with streptavidin coated paramagnetic beads and retrieving the beads with a magnet. Thereafter, the resulting phagemids containing the 5' EST sequence are released from the beads and converted into double stranded DNA using a primer specific for the 5' EST sequence. The resulting double stranded DNA is transformed into bacteria. Extended cDNAs containing the 5' EST sequence are identified by colony PCR or colony hybridization.

A plurality of extended cDNAs containing full length protein coding sequences or sequences encoding only the mature protein remaining after the signal peptide is cleaved may be provided as cDNA libraries for subsequent evaluation of the encoded proteins or use in diagnostic assays as described below.

IV. Expression of Proteins Encoded by Extended cDNAs Isolated Using 5' ESTs

Extended cDNAs containing the full protein coding sequences of their corresponding mRNAs or portions

thereof, such as cDNAs encoding the mature protein, may be used to express the secreted proteins or portions thereof which they encode as described in Example 30 below. If desired, the extended cDNAs may contain the sequences encoding the signal peptide to facilitate secretion of the expressed protein. It will be appreciated that a plurality of extended cDNAs containing the full protein coding sequences or portions thereof may be simultaneously cloned into expression vectors to create an expression library for analysis of the encoded proteins as described below.

30 EXAMPLE 30

Expression of the Proteins Encoded by Extended cDNAs or Portions Thereof

To express the proteins encoded by the extended cDNAs or portions thereof, nucleic acids containing the coding sequence for the proteins or portions thereof to be expressed are obtained as described in Examples 27-29 and cloned into a suitable expression vector. If desired, the nucleic acids may contain the sequences encoding the signal

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peptide to facilitate secretion of the expressed protein. For example, the nucleic acid may comprise the sequence of one of SEQ ID NOs: 40-140 and 242-377 listed in Table IV and in the accompanying sequence listing. Alternatively, the nucleic acid may comprise those nucleotides which make up the full coding sequence of one of the sequences of SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above.

5 It will be appreciated that should the extent of the full coding sequence (i.e. the sequence encoding the signal peptide and the mature protein resulting from cleavage of the signal peptide) differ from that listed in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the full coding sequences in the sequences of SEQ ID NOs. 40-140 and 242-377. 10 For example, the sequence of SEQ ID NO: 115 represents an alternatively spliced transcript of a previously identified mRNA.. Accordingly, the scope of any claims herein relating to nucleic acids containing the full coding sequence of one of SEQ ID NOs. 40-140 and 242-377 is not to be construed as excluding any readily identifiable variations from or equivalents to the full coding sequences listed in Table IV Similarly, should the extent of the full length polypeptides differ from those indicated in Table V as a result of any of the preceding factors, the scope of claims relating to polypeptides 15 comprising the amino acid sequence of the full length polypeptides is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table V.

Alternatively, the nucleic acid used to express the protein or portion thereof may comprise those nucleotides which encode the mature protein (i.e. the protein created by cleaving the signal peptide off) encoded by one of the sequences of SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above.

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It will be appreciated that should the extent of the sequence encoding the mature protein differ from that listed in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, posttranslational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the sequence encoding the mature protein in the sequences of SEQ ID NOs. 40-140 and 242-377. Accordingly, the scope of any claims herein relating to nucleic acids 25 containing the sequence encoding the mature protein encoded by one of SEQ ID Nos. 40-140 and 242-377 is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table IV. Thus, claims relating to nucleic acids containing the sequence encoding the mature protein encompass equivalents to the sequences listed in Table IV, such as sequences encoding biologically active proteins resulting from post-translational modification, enzymatic cleavage, or other readily identifiable variations from or equivalents to the secreted proteins in 30 addition to cleavage of the signal peptide. Similarly, should the extent of the mature polypeptides differ from those indicated in Table V as a result of any of the preceding factors, the scope of claims relating to polypeptides comprising the sequence of a mature protein included in the sequence of one of SEQ ID NOs. 141-241 and 378-513 is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table V. Thus, claims relating to polypeptides comprising the sequence of the mature protein encompass equivalents to the sequences

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listed in Table IV, such as biologically active proteins resulting from post-translational modification, enzymatic cleavage, or other readily identifiable variations from or equivalents to the secreted proteins in addition to cleavage of the signal peptide. It will also be appreciated that should the biologically active form of the polypeptides included in the sequence of one of SEQ IO NOs. 141-241 and 378-513 or the nucleic acids encoding the biologically active form of the polypeptides differ from those identified as the mature polypeptide in Table V or the nucleotides encoding the mature polypeptide in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the amino acids in the biologically active form of the polypeptides and the nucleic acids encoding the biologically active form of the polypeptides. In such instances, the claims relating to polypetides comprising the mature protein included in one of SEQ ID NOs. 141-241 and 378-513 or nucleic acids comprising the nucleotides of one of SEQ ID NOs. 40-140 and 242-377 encoding the mature protein shall not be construed to exclude any readily identifiable variations from the sequences listed in Table IV and Table V.

In some embodiments, the nucleic acid used to express the protein or portion thereof may comprise those nucleotides which encode the signal peptide encoded by one of the sequences of SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above.

It will be appreciated that should the extent of the sequence encoding the signal peptide differ from that listed in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the sequence encoding the signal peptide in the sequences of SEQ ID Nos. 40·140 and 242·377. Accordingly, the scope of any claims herein relating to nucleic acids containing the sequence encoding the signal peptide encoded by one of SEQ ID Nos. 40·140 and 242·377 is not to be construed as excluding any readily identifiable variations from the sequences listed in Table IV. Similarly, should the extent of the signal peptides differ from those indicated in Table V as a result of any of the preceding factors, the scope of claims relating to polypeptides comprising the sequence of a signal peptide included in the sequence of one of SEQ ID NOs. 141-241 and 378·513 is not to be construed as excluding any readily identifiable variations from the sequences listed in Table V.

Alternatively, the nucleic acid may encode a polypeptide comprising at least 10 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In some embodiments, the nucleic acid may encode a polypeptide comprising at least 15 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-30. In other embodiments, the nucleic acid may encode a polypeptide comprising at least 25 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In other embodiments, the nucleic acid may encode a polypeptide comprising at least 60, at least 75, at least 100 or more than 100 consecutive amino acids of one of the sequences of SEQ ID Nos: 141-241 and 378-513.

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The nucleic acids inserted into the expression vectors may also contain sequences upstream of the sequences encoding the signal peptide, such as sequences which regulate expression levels or sequences which confer tissue specific expression.

The nucleic acid encoding the protein or polypeptide to be expressed is operably linked to a promoter in an expression vector using conventional cloning technology. The expression vector may be any of the mammalian, yeast, insect or bacterial expression systems known in the art. Commercially available vectors and expression systems are available from a variety of suppliers including Genetics Institute (Cambridge, MA), Stratagene (La Jolla, California), Promega (Madison, Wisconsin), and Invitrogen (San Diego, California). If desired, to enhance expression and facilitate proper protein folding, the codon context and codon pairing of the sequence may be optimized for the particular expression organism in which the expression vector is introduced, as explained by Hatfield, et al., U.S. Patent No. 5,082,767.

The following is provided as one exemplary method to express the proteins encoded by the extended cDNAs corresponding to the 5' ESTs or the nucleic acids described above. First, the methionine initiation codon for the gene and the poly A signal of the gene are identified. If the nucleic acid encoding the polypeptide to be expressed lacks a methionine to serve as the initiation site, an initiating methionine can be introduced next to the first codon of the nucleic acid using conventional techniques. Similarly, if the extended cDNA lacks a poly A signal, this sequence can be added to the construct by, for example, splicing out the Poly A signal from pSG5 (Stratagene) using Bgll and Sall restriction endonuclease enzymes and incorporating it into the mammalian expression vector pXT1 (Stratagene). pXT1 contains the LTRs and a portion of the gag gene from Moloney Murine Leukemia Virus. The position of the LTRs in the construct allow efficient stable transfection. The vector includes the Herpes Simplex Thymidine Kinase promoter and the selectable neomycin gene. The extended cDNA or portion thereof encoding the polypeptide to be expressed is obtained by PCR from the bacterial vector using oligonucleotide primers complementary to the extended cDNA or portion thereof and containing restriction endonuclease sequences for Pst I incorporated into the 5' primer and Bglll at the 5' end of the corresponding cDNA 3' primer, taking care to ensure that the extended cDNA is positioned in frame with the poly A signal. The purified fragment obtained from the resulting PCR reaction is digested with Pstl, blunt ended with an exonuclease, digested with BgllI, purified and ligated to pXT1, now containing a poly A signal and digested with BgllI.

The ligated product is transfected into mouse NIH 3T3 cells using Lipofectin (Life Technologies, Inc., Grand Island, New York) under conditions outlined in the product specification. Positive transfectants are selected after growing the transfected cells in 600ug/ml G418 (Sigma, St. Louis, Missouri). Preferably the expressed protein is released into the culture medium, thereby facilitating purification.

Alternatively, the extended cDNAs may be cloned into pED6dpc2 as described above. The resulting pED6dpc2 constructs may be transfected into a suitable host cell, such as COS 1 cells. Methotrexate resistant cells are selected and expanded. Preferably, the protein expressed from the extended cDNA is released into the culture medium thereby facilitating purification.

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Proteins in the culture medium are separated by gel electrophoresis. If desired, the proteins may be ammonium sulfate precipitated or separated based on size or charge prior to electrophoresis.

As a control, the expression vector lacking a cDNA insert is introduced into host cells or organisms and the proteins in the medium are harvested. The secreted proteins present in the medium are detected using techniques such as Coomassie or silver staining or using antibodies against the protein encoded by the extended cDNA. Coomassie and silver staining techniques are familiar to those skilled in the art.

Antibodies capable of specifically recognizing the protein of interest may be generated using synthetic 15-mer peptides having a sequence encoded by the appropriate 5' EST, extended cDNA, or portion thereof. The synthetic peptides are injected into mice to generate antibody to the polypeptide encoded by the 5' EST, extended cDNA, or portion thereof.

Secreted proteins from the host cells or organisms containing an expression vector which contains the extended cDNA derived from a 5' EST or a portion thereof are compared to those from the control cells or organism. The presence of a band in the medium from the cells containing the expression vector which is absent in the medium from the control cells indicates that the extended cDNA encodes a secreted protein. Generally, the band corresponding to the protein encoded by the extended cDNA will have a mobility near that expected based on the number of amino acids in the open reading frame of the extended cDNA. However, the band may have a mobility different than that expected as a result of modifications such as glycosylation, ubiquitination, or enzymatic cleavage.

Alternatively, if the protein expressed from the above expression vectors does not contain sequences directing its secretion, the proteins expressed from host cells containing an expression vector containing an insert encoding a secreted protein or portion thereof can be compared to the proteins expressed in host cells containing the expression vector without an insert. The presence of a band in samples from cells containing the expression vector with an insert which is absent in samples from cells containing the expression vector without an insert indicates that the desired protein or portion thereof is being expressed. Generally, the band will have the mobility expected for the secreted protein or portion thereof. However, the band may have a mobility different than that expected as a result of modifications such as glycosylation, ubiquitination, or enzymatic cleavage.

The protein encoded by the extended cDNA may be purified using standard immunochromatography techniques. In such procedures, a solution containing the secreted protein, such as the culture medium or a cell extract, is applied to a column having antibodies against the secreted protein attached to the chromatography matrix. The secreted protein is allowed to bind the immunochromatography column. Thereafter, the column is washed to remove non-specifically bound proteins. The specifically bound secreted protein is then released from the column and recovered using standard techniques.

If antibody production is not possible, the extended cDNA sequence or portion thereof may be incorporated into expression vectors designed for use in purification schemes employing chimeric polypeptides. In such strategies the coding sequence of the extended cDNA or portion thereof is inserted in frame with the gene encoding the other half of

the chimera. The other half of the chimera may be β-globin or a nickel binding polypeptide encoding sequence. A chromatography matrix having antibody to β-globin or nickel attached thereto is then used to purify the chimeric protein. Protease cleavage sites may be engineered between the β-globin gene or the nickel binding polypeptide and the extended cDNA or portion thereof. Thus, the two polypeptides of the chimera may be separated from one another by protease digestion.

One useful expression vector for generating β-globin chimerics is pSG5 (Stratagene), which encodes rabbit β-globin. Intron II of the rabbit β-globin gene facilitates splicing of the expressed transcript, and the polyadenylation signal incorporated into the construct increases the level of expression. These techniques as described are well known to those skilled in the art of molecular biology. Standard methods are published in methods texts such as Davis et al.,

(Basic Methods in Molecular Biology, L.G. Davis, M.D. Dibner, and J.F. Battey, ed., Elsevier Press, NY, 1986) and many of the methods are available from Stratagene, Life Technologies, Inc., or Promega. Polypeptide may additionally be produced from the construct using in vitro translation systems such as the In vitro ExpressTM Translation Kit (Stratagene).

Following expression and purification of the secreted proteins encoded by the 5' ESTs, extended cDNAs, or fragments thereof, the purified proteins may be tested for the ability to bind to the surface of various cell types as described in Example 31 below. It will be appreciated that a plurality of proteins expressed from these cDNAs may be included in a panel of proteins to be simultaneously evaluated for the activities specifically described below, as well as other biological roles for which assays for determining activity are available.

EXAMPLE 31

Analysis of Secreted Proteins to Determine Whether they Bind to the Cell Surface

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The proteins encoded by the 5' ESTs, extended cDNAs, or fragments thereof are cloned into expression vectors such as those described in Example 30. The proteins are purified by size, charge, immunochromatography or other techniques familiar to those skilled in the art. Following purification, the proteins are labeled using techniques known to those skilled in the art. The labeled proteins are incubated with cells or cell lines derived from a variety of organs or tissues to allow the proteins to bind to any receptor present on the cell surface. Following the incubation, the cells are washed to remove non-specifically bound protein. The labeled proteins are detected by autoradiography. Alternatively, unlabeled proteins may be incubated with the cells and detected with antibodies having a detectable label, such as a fluorescent molecule, attached thereto.

Specificity of cell surface binding may be analyzed by conducting a competition analysis in which various

amounts of unlabeled protein are incubated along with the labeled protein. The amount of labeled protein bound to the cell surface decreases as the amount of competitive unlabeled protein increases. As a control, various amounts of an unlabeled protein unrelated to the labeled protein is included in some binding reactions. The amount of labeled protein bound to the cell surface does not decrease in binding reactions containing increasing amounts of unrelated unlabeled protein, indicating that the protein encoded by the cDNA binds specifically to the cell surface.

As discussed above, secreted proteins have been shown to have a number of important physiological effects and, consequently, represent a valuable therapeutic resource. The secreted proteins encoded by the extended cDNAs or portions thereof made according to Examples 27-29 may be evaluated to determine their physiological activities as described below.

5 EXAMPLE 32

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Cytokine, Cell Proliferation or Cell Differentiation Activity

As discussed above, secreted proteins may act as cytokines or may affect cellular proliferation or differentiation. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B5, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7c and CMK. The proteins encoded by the above extended cDNAs or portions thereof may be evaluated for their ability to regulate T cell or thymocyte proliferation in assays such as those described above or in the following references: Current Protocols in Immunology, Ed. by J.E. Coligan et al., Greene Publishing Associates and Wiley-Interscience; Takai et al. J. Immunol. 137:3494-3500, 1986. Bertagnolli et al. J. Immunol. 145:1706-1712, 1990. Bertagnolli et al., Cellular Immunology 133:327-341, 1991. Bertagnolli, et al. J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152:1756-1761, 1994.

In addition, numerous assays for cytokine production and/or the proliferation of spleen cells, lymph node cells
and thymocytes are known. These include the techniques disclosed in Current Protocols in Immunology. J.E. Coligan
et al. Eds., Vol 1 pp. 3.12.1-3.12.14 John Wiley and Sons, Toronto. 1994; and Schreiber, R.D. Current Protocols in
Immunology., supra Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

The proteins encoded by the cDNAs may also be assayed for the ability to regulate the proliferation and differentiation of hematopoietic or lymphopoietic cells. Many assays for such activity are familiar to those skilled in the art, including the assays in the following references: Bottomly, K., Davis, L.S. and Lipsky, P.E., Measurement of Human and Murine Interleukin 2 and Interleukin 4, Current Protocols in Immunology., J.E. Coligan et al. Eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 36:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Nordan, R., Measurement of Mouse and Human Interleukin 6 Current Protocols in Immunology. J.E. Coligan et al. Eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Bennett, F., Giannotti, J., Clark, S.C. and Turner, K.J., Measurement of Human Interleukin 11 Current Protocols in Immunology. J.E. Coligan et al. Eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J., Measurement of Mouse and Human Interleukin 9 Current Protocols in Immunology. J.E. Coligan et al., Eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

The proteins encoded by the cDNAs may also be assayed for their ability to regulate T-cell responses to antigens. Many assays for such activity are familiar to those skilled in the art, including the assays described in the following references: Chapter 3 (In Vitro Assays for Mouse Lymphocyte Function), Chapter 6 (Cytokines and Their Cellular Receptors) and Chapter 7, (Immunologic Studies in Humans) in Current Protocols in Immunology, J.E. Coligan et al. Eds. Greene Publishing Associates and Wiley-Interscience; Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Those proteins which exhibit cytokine, cell proliferation, or cell differentiation activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which induction of cell proliferation or differentiation is beneficial. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 33

Assaying the Proteins Expressed from Extended cDNAs or Portions

15 <u>Thereof for Activity as Immune System Regulators</u>

The proteins encoded by the cDNAs may also be evaluated for their effects as immune regulators. For example, the proteins may be evaluated for their activity to influence thymocyte or splenocyte cytotoxicity. Numerous assays for such activity are familiar to those skilled in the art including the assays described in the following references: Chapter 3 (In Vitro Assays for Mouse Lymphocyte Function 3.1-3.19) and Chapter 7 (Immunologic studies in Humans) in Current Protocols in Immunology, J.E. Coligan et al. Eds, Greene Publishing Associates and Wiley-Interscience; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

The proteins encoded by the cDNAs may also be evaluated for their effects on T-cell dependent immunoglobulin responses and isotype switching. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Maliszewski, J. Immunol. 144:3028-3033, 1990; Mond, J.J. and Brunswick, M Assays for B Cell Function: *In vitro* Antibody Production, Vol 1 pp. 3.8.1-3.8.16 in Current Protocols in Immunology. J.E. Coligan et al Eds., John Wiley and Sons, Toronto. 1994.

The proteins encoded by the cDNAs may also be evaluated for their effect on immune effector cells, including their effect on Th1 cells and cytotoxic lymphocytes. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Chapter 3 (In Vitro Assays for Mouse Lymphocyte

Function 3.1-3.19) and Chapter 7 (Immunologic Studies in Humans) in **Current Protocols in Immunology**, J.E. Coligan et al. Eds., Greene Publishing Associates and Wiley-Interscience; Takai et al., **J. Immunol.** 137:3494-3500, 1986; Takai et al.; **J. Immunol.** 140:508-512, 1988; Bertagnolli et al., **J. Immunol.** 149:3778-3783, 1992.

The proteins encoded by the cDNAs may also be evaluated for their effect on dendritic cell mediated activation
of naive T-cells. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264,
10 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

The proteins encoded by the cDNAs may also be evaluated for their influence on the lifetime of lymphocytes.

Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Those proteins which exhibit activity as immune system regulators activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of immune activity is beneficial. For example, the protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCIO)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases caused by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis,

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myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to regulate immune responses, in a number of ways.

Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T-cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent.

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Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte

antigen functions (such as, for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will

be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example,

blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue

transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune

reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7

lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7
activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen

(e.g., B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural

ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte

antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an

immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing

tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the

necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance

in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models

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of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function in vivo on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which 5 promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead 10 to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/pr/pr mice or NZB hybrid mice, murine autoimmuno collagen arthritis, diabetes mellitus in OD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory 20 form of B lymphocyte antigens systemically.

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Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to T cells 25 in vivo, thereby activating the T cells.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (e.g., sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be 30 transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected ex vivo with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection in vivo.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acids encoding all or a portion of (e.g., a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β₂ macroglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class II or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 34

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Hematopoiesis Regulating Activity

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their hematopoiesis regulating activity. For example, the effect of the proteins on embryonic stem cell differentiation may be evaluated.

Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their influence on the lifetime of stem cells and stem cell differentiation. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Freshney, M.G. Methylcellulose Colony Forming Assays, in Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds. pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; McNiece, I.K. and Briddell, R.A. Primitive Hematopoietic Colony Forming Cells with High Proliferative Potential, in Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Ploemacher, R.E. Cobblestone Area Forming Cell Assay, In Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds. pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Spooncer, E., Dexter, M. and Allen, T. Long Term Bone Marrow Cultures in the Presence of Stromal Cells, in Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds.

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pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; and Sutherland, H.J. Long Term Culture Initiating Cell Assay, in **Culture of Hematopoietic Cells**. R.I. Freshney, et al. Eds. pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Those proteins which exhibit hematopoiesis regulatory activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of hematopoeisis is beneficial. For example, a protein of the present 5 invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid 10 cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelosuppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem 15 cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantion, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vivo or ex-vivo (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or 20 genetically manipulated for gene therapy. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 35

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Regulation of Tissue Growth

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their effect on tissue growth. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in International Patent Publication No. W095/16035, International Patent Publication No. W095/05846 and International Patent Publication No. W091/07491.

Assays for wound healing activity include, without limitation, those described in: Winter, <u>Epidermal Wound</u>

30 <u>Healing</u>, pps. 71-112 (Maibach, H1 and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Those proteins which are involved in the regulation of tissue growth may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of tissue growth is beneficial. For example, a protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or

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nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

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Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to 20 tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate 25 growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors ex vivo for return in vivo to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of 30 nerve and brain tissue, i.e., for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium) muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to generate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokinc damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

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EXAMPLE 36

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Regulation of Reproductive Hormones or Cell Movement

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their ability to regulate reproductive hormones, such as follicle stimulating hormone. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986. Chapter 6.12 (Measurement of Alpha and Beta Chemokines) Current Protocols in Immunology, J.E. Coligan et al. Eds. Greene Publishing Associates and Wiley-Intersciece; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al. Eur. J. Immunol. 25:1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153:1762-1768, 1994.

Those proteins which exhibit activity as reproductive hormones or regulators of cell movement may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of reproductive hormones or cell movement are beneficial. For example, a protein of the present invention may also exhibit activin- or inhibin-related

activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins are characterized by their ability to stimulate the release of folic stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals.
Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin B group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive
performance of domestic animals such as cows, sheep and pigs.

Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 36A

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Assaving the Proteins Expressed from Extended cDNAs or Portions Thereof for Chemotactic/Chemokinetic Activity

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for chemotactic/chemokinetic activity. For example, a protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, cosinophils, epithelial and/or endothelial cells. Chemotactic and chmokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhension of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12,

Measurement of alpha and beta Chemokincs 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Mueller et al Eur. J. Immunol. 25:1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol, 153:1762-1768, 1994.

EXAMPLE 37

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Assaying the Proteins Expressed from Extended cDNAs or

Portions Thereof for Regulation of Blood Clotting

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their effects on blood clotting. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Linet et al., **J. Clin. Pharmacol.** 26:131-140, 1986; Burdick et al., **Thrombosis Res.**45:413-419, 1987; Humphrey et al., **Fibrinolysis** 5:71-79 (1991); Schaub, **Prostaglandins** 35:467-474, 1988.

Those proteins which are involved in the regulation of blood clotting may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of blood clotting is beneficial. For example, a protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulations disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke). Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 38

Assaying the Proteins Expressed from Extended cDNAs or

Portions Thereof for Involvement in Receptor/Ligand Interactions

The proteins encoded by the extended cDNAs or a portion thereof may also be evaluated for their involvement in receptor/ligand interactions. Numerous assays for such involvement are familiar to those skilled in the art, including the assays disclosed in the following references: Chapter 7.28 (Measurement of Cellular Adhesion under Static Conditions 7.28.1-7.28.22) in Current Protocols in Immunology, J.E. Coligan et al. Eds. Greene Publishing Associates and Wiley-Interscience; Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160, 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995; Gyuris et al., Cell 75:791-803, 1993.

For example, the proteins of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion

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molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune respones). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

EXAMPLE 38A

Assaying the Proteins Expressed from Extended cDNAs or Portions

Thereof for Anti-Inflammatory Activity

The proteins encoded by the extended cDNAs or a portion thereof may also be evaluated for anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusioninury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

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EXAMPLE 38B

Assaying the Proteins Expressed from Extended cDNAs or

Portions Thereof for Tumor Inhibition Activity

The proteins encoded by the extended cDNAs or a portion thereof may also be evaluated for tumor inhibition activity. In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, climinating or inhibiting factors, agents or cell types which promote tumor growth.

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or

circadian cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or climination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

EXAMPLE 39

Identification of Proteins which Interact with

Polypeptides Encoded by Extended cDNAs

Proteins which interact with the polypeptides encoded by extended cDNAs or portions thereof, such as

receptor proteins, may be identified using two hybrid systems such as the Matchmaker Two Hybrid System 2 (Catalog No. K1604-1, Clontech). As described in the manual accompanying the Matchmaker Two Hybrid System 2 (Catalog No. K1604-1, Clontech), the extended cDNAs or portions thereof, are inserted into an expression vector such that they are in frame with DNA encoding the DNA binding domain of the yeast transcriptional activator GAL4. cDNAs in a cDNA library which encode proteins which might interact with the polypeptides encoded by the extended cDNAs or portions thereof

are inserted into a second expression vector such that they are in frame with DNA encoding the activation domain of GAL4. The two expression plasmids are transformed into yeast and the yeast are plated on selection medium which selects for expression of selectable markers on each of the expression vectors as well as GAL4 dependent expression of the HIS3 gene. Transformants capable of growing on medium lacking histidine are screened for GAL4 dependent lacZ expression. Those cells which are positive in both the histidine selection and the lacZ assay contain plasmids encoding proteins which interact with the polypeptide encoded by the extended cDNAs or portions thereof.

Alternatively, the system described in Lustig et al., Methods in Enzymology 283: 83-99 (1997) may be used for identifying molecules which interact with the polypeptides encoded by extended cDNAs. In such systems, in vitro transcription reactions are performed on a pool of vectors containing extended cDNA inserts cloned downstream of a promoter which drives in vitro transcription. The resulting pools of mRNAs are introduced into Xenopus laevis oocytes.

30 The oocytes are then assayed for a desired activity.

Alternatively, the pooled *in vitro* transcription products produced as described above may be translated *in vitro*. The pooled *in vitro* translation products can be assayed for a desired activity or for interaction with a known polypeptide.

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Proteins or other molecules interacting with polypeptides encoded by extended cDNAs can be found by a variety of additional techniques. In one method, affinity columns containing the polypeptide encoded by the extended cDNA or a portion thereof can be constructed. In some versions, of this method the affinity column contains chimeric proteins in which the protein encoded by the extended cDNA or a portion thereof is fused to glutathione S-transferase.

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5 A mixture of cellular proteins or pool of expressed proteins as described above and is applied to the affinity column. Proteins interacting with the polypeptide attached to the column can then be isolated and analyzed on 2-D electrophoresis gel as described in Ramunsen et al. Electrophoresis, 18, 588-598 (1997). Alternatively, the proteins retained on the affinity column can be purified by electrophoresis based methods and sequenced. The same method can be used to isolate antibodies, to screen phage display products, or to screen phage display human antibodies.

Proteins interacting with polypeptides encoded by extended cDNAs or portions thereof can also be screened by using an Optical Biosensor as described in Edwards & Leatherbarrow, Analytical Biochemistry, 246, 1-6 (1997). The main advantage of the method is that it allows the determination of the association rate between the protein and other interacting molecules. Thus, it is possible to specifically select interacting molecules with a high or low association rate. Typically a target molecule is linked to the sensor surface (through a carboxymethl dextran matrix) and a sample of test 15 molecules is placed in contact with the target molecules. The binding of a test molecule to the target molecule causes a change in the refractive index and/ or thickness. This change is detected by the Biosensor provided it occurs in the evanescent field (which extend a few hundred manometers from the sensor surface). In these screening assays, the target molecule can be one of the polypeptides encoded by extended cDNAs or a portion thereof and the test sample can be a collection of proteins extracted from tissues or cells, a pool of expressed proteins, combinatorial peptide and/ or 20 chemical libraries,or phage displayed peptides. The tissues or cells from which the test proteins are extracted can originate from any species.

In other methods, a target protein is immobilized and the test population is a collection of unique polypeptides encoded by the extended cDNAs or portions thereof.

To study the interaction of the proteins encoded by the extended cDNAs or portions thereof with drugs, the 25 microdialysis coupled to HPLC method described by Wang et al., Chromatographia, 44, 205-208(1997) or the affinity capillary electrophoresis method described by Busch et al., J. Chromatogr. 777:311-328 (1997), the disclosures of which are incorporated herein by referenc can be used.

The system described in U.S. Patent No. 5,654,150 may also be used to identify molecules which interact with the polypeptides encoded by the extended cDNAs. In this system, pools of extended cDNAs are transcribed and 30 translated in vitro and the reaction products are assayed for interaction with a known polypeptide or antibody.

It will be appreciated by those skilled in the art that the proteins expressed from the extended cDNAs or portions may be assayed for numerous activities in addition to those specifically enumerated above. For example, the expressed proteins may be evaluated for applications involving control and regulation of inflammation, tumor

proliferation or metastasis, infection, or other clinical conditions. In addition, the proteins expressed from the extended cDNAs or portions thereof may be useful as nutritional agents or cosmetic agents.

The proteins expressed from the extended cDNAs or portions thereof may be used to generate antibodies capable of specifically binding to the expressed protein or fragments thereof as described in Example 40 below. The antibodies may capable of binding a full length protein encoded by one of the sequences of SEO ID NOs. 40-140 and 242-377, a mature protein encoded by one of the sequences of SEO ID NOs. 40-140 and 242-377, or a signal peptide encoded by one of the sequences of SEO ID Nos. 40-140 and 242-377. Alternatively, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 10 amino acids of the sequences of SEO ID NOs: 141-241 and 378-513. In some embodiments, the antibodies may be capable of binding fragments of SEO ID NOs: 141-241 and 378-513. In other embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 15 amino acids of the sequences of SEO ID NOs: 141-241 and 378-513. In further embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 25 amino acids of the sequences of SEO ID NOs: 141-241 and 378-513. In further embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 40 amino acids of the sequences of SEO ID NOs: 141-241 and 378-513.

EXAMPLE 40

Production of an Antibody to a Human Protein

Substantially pure protein or polypeptide is isolated from the transfected or transformed cells as described in Example 30. The concentration of protein in the final preparation is adjusted, for example, by concentration on an Amicon filter device, to the level of a few micrograms/ml. Monoclonal or polyclonal antibody to the protein can then be prepared as follows:

A. Monoclonal Antibody Production by Hybridoma Fusion

Monoclonal antibody to epitopes of any of the peptides identified and isolated as described can be prepared from murine hybridomas according to the classical method of Kohler, G. and Milstein, C., Nature 256:495 (1975) or derivative methods thereof. Briefly, a mouse is repetitively inoculated with a few micrograms of the selected protein or peptides derived therefrom over a period of a few weeks. The mouse is then sacrificed, and the antibody producing cells of the spleen isolated. The spleen cells are fused by means of polyethylene glycol with mouse myeloma cells, and the excess unfused cells destroyed by growth of the system on selective media comprising aminopterin (HAT media). The successfully fused cells are diluted and aliquots of the dilution placed in wells of a microtiter plate where growth of the culture is continued. Antibody producing clones are identified by detection of antibody in the supernatant fluid of the wells by immunoassay procedures, such as Elisa, as originally described by Engvall, E., Meth. Enzymol. 70:419 (1980), and derivative methods thereof. Selected positive clones can be expanded and their monoclonal antibody product harvested for use. Detailed procedures for monoclonal antibody production are described in Davis, L. et al. Basic Methods in Molecular Biology Elsevier, New York. Section 21-2.

B. Polyclonal Antibody Production by Immunization

Polyclonal antiserum containing antibodies to heterogenous epitopes of a single protein can be prepared by immunizing suitable animals with the expressed protein or peptides derived therefrom described above, which can be unmodified or modified to enhance immunogenicity. Effective polyclonal antibody production is affected by many factors related both to the antigen and the host species. For example, small molecules tend to be less immunogenic than others and may require the use of carriers and adjuvant. Also, host animals vary in response to site of inoculations and dose, with both inadequate or excessive doses of antigen resulting in low titer antisera. Small doses (ng level) of antigen administered at multiple intradermal sites appears to be most reliable. An effective immunization protocol for rabbits can be found in Vaitukaitis, J. et al. J. Clin. Endocrinol. Metab. 33:988-991 (1971).

Booster injections can be given at regular intervals, and antiserum harvested when antibody titer thereof, as determined semi-quantitatively, for example, by double immunodiffusion in agar against known concentrations of the antigen, begins to fall. See, for example, Ouchterlony, O. et al., Chap. 19 in: Handbook of Experimental Immunology D. Wier (ed) Blackwell (1973). Plateau concentration of antibody is usually in the range of 0.1 to 0.2 mg/ml of serum (about 12 μM). Affinity of the antisera for the antigen is determined by preparing competitive binding curves, as described, for example, by Fisher, D., Chap. 42 in: Manual of Clinical Immunology, 2d Ed. (Rose and Friedman, Eds.) Amer. Soc. For Microbiol., Washington, D.C. (1980).

Antibody preparations prepared according to either protocol are useful in quantitative immunoassays which determine concentrations of antigen-bearing substances in biological samples; they are also used semi-quantitatively or qualitatively to identify the presence of antigen in a biological sample. The antibodies may also be used in therapeutic compositions for killing cells expressing the protein or reducing the levels of the protein in the body.

V. Use of Extended cDNAs or Portions Thereof as Reagents

The extended cDNAs of the present invention may be used as reagents in isolation procedures, diagnostic assays, and forensic procedures. For example, sequences from the extended cDNAs (or genomic DNAs obtainable therefrom) may be detectably labeled and used as probes to isolate other sequences capable of hybridizing to them. In addition, sequences from the extended cDNAs (or genomic DNAs obtainable therefrom) may be used to design PCR primers to be used in isolation, diagnostic, or forensic procedures.

EXAMPLE 41

Preparation of PCR Primers and Amplification of DNA

The extended cDNAs (or genomic DNAs obtainable therefrom) may be used to prepare PCR primers for a variety of applications, including isolation procedures for cloning nucleic acids capable of hybridizing to such sequences, diagnostic techniques and forensic techniques. The PCR primers are at least 10 bases, and preferably at least 12, 15, or 17 bases in length. More preferably, the PCR primers are at least 20-30 bases in length. In some embodiments, the PCR primers may be more than 30 bases in length. It is preferred that the primer pairs have approximately the same G/C

ratio, so that melting temperatures are approximately the same. A variety of PCR techniques are familiar to those skilled in the art. For a review of PCR technology, see Molecular Cloning to Genetic Engineering White, B.A. Ed. in Methods in Molecular Biology 67: Humana Press, Totowa 1997. In each of these PCR procedures, PCR primers on either side of the nucleic acid sequences to be amplified are added to a suitably prepared nucleic acid sample along with dNTPs and a thermostable polymerase such as Taq polymerase, Pfu polymerase, or Vent polymerase. The nucleic acid in the sample is denatured and the PCR primers are specifically hybridized to complementary nucleic acid sequences in the sample. The hybridized primers are extended. Thereafter, another cycle of denaturation, hybridization, and extension is initiated. The cycles are repeated multiple times to produce an amplified fragment containing the nucleic acid sequence between the primer sites.

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EXAMPLE 42

Use of Extended cDNAs as Probes

Probes derived from extended cDNAs or portions thereof (or genomic DNAs obtainable therefrom) may be labeled with detectable labels familiar to those skilled in the art, including radioisotopes and non-radioactive labels, to provide a detectable probe. The detectable probe may be single stranded or double stranded and may be made using techniques known in the art, including in vitro transcription, nick translation, or kinase reactions. A nucleic acid sample containing a sequence capable of hybridizing to the labeled probe is contacted with the labeled probe. If the nucleic acid in the sample is double stranded, it may be denatured prior to contacting the probe. In some applications, the nucleic acid sample may be immobilized on a surface such as a nitrocellulose or nylon membrane. The nucleic acid sample may comprise nucleic acids obtained from a variety of sources, including genomic DNA, cDNA libraries, RNA, or tissue samples.

Procedures used to detect the presence of nucleic acids capable of hybridizing to the detectable probe include well known techniques such as Southern blotting, Northern blotting, dot blotting, colony hybridization, and plaque hybridization. In some applications, the nucleic acid capable of hybridizing to the labeled probe may be cloned into vectors such as expression vectors, sequencing vectors, or in vitro transcription vectors to facilitate the characterization and expression of the hybridizing nucleic acids in the sample. For example, such techniques may be used to isolate and clone sequences in a genomic library or cDNA library which are capable of hybridizing to the detectable probe as described in Example 30 above.

PCR primers made as described in Example 41 above may be used in forensic analyses, such as the DNA fingerprinting techniques described in Examples 43-47 below. Such analyses may utilize detectable probes or primers based on the sequences of the extended cDNAs isolated using the 5' ESTs (or genomic DNAs obtainable therefrom).

EXAMPLE 43

Forensic Matching by DNA Sequencing

In one exemplary method, DNA samples are isolated from forensic specimens of, for example, hair, semen, blood or skin cells by conventional methods. A panel of PCR primers based on a number of the extended cDNAs (or

genomic DNAs obtainable therefrom), is then utilized in accordance with Example 41 to amplify DNA of approximately 100-200 bases in length from the forensic specimen. Corresponding sequences are obtained from a test subject. Each of these identification DNAs is then sequenced using standard techniques, and a simple database comparison determines the differences, if any, between the sequences from the subject and those from the sample. Statistically significant differences between the suspect's DNA sequences and those from the sample conclusively prove a lack of identity. This lack of identity can be proven, for example, with only one sequence. Identity, on the other hand, should be demonstrated with a large number of sequences, all matching. Preferably, a minimum of 50 statistically identical sequences of 100 bases in length are used to prove identity between the suspect and the sample.

EXAMPLE 44

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Positive Identification by DNA Sequencing

The technique outlined in the previous example may also be used on a larger scale to provide a unique fingerprint-type identification of any individual. In this technique, primers are prepared from a large number of sequences from Table IV and the appended sequence listing. Preferably, 20 to 50 different primers are used. These primers are used to obtain a corresponding number of PCR-generated DNA segments from the individual in question in accordance with Example 41. Each of these DNA segments is sequenced, using the methods set forth in Example 43. The database of sequences generated through this procedure uniquely identifies the individual from whom the sequences were obtained. The same panel of primers may then be used at any later time to absolutely correlate tissue or other biological specimen with that individual.

EXAMPLE 45

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Southern Blot Forensic Identification

The procedure of Example 44 is repeated to obtain a panel of at least 10 amplified sequences from an individual and a specimen. Preferably, the panel contains at least 50 amplified sequences. More preferably, the panel contains 100 amplified sequences. In some embodiments, the panel contains 200 amplified sequences. This PCR-generated DNA is then digested with one or a combination of, preferably, four base specific restriction enzymes. Such enzymes are commercially available and known to those of skill in the art. After digestion, the resultant gene fragments are size separated in multiple duplicate wells on an agarose gel and transferred to nitrocellulose using Southern blotting techniques well known to those with skill in the art. For a review of Southern blotting see Davis et al. (Basic Methods in Molecular Biology, 1986, Elsevier Press. pp 62-65).

A panel of probes based on the sequences of the extended cDNAs (or genomic DNAs obtainable therefrom), or fragments thereof of at least 10 bases, are radioactively or colorimetrically labeled using methods known in the art, such as nick translation or end labeling, and hybridized to the Southern blot using techniques known in the art (Davis et al., supra). Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). More preferably, the probe comprises at least 20-30 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In some embodiments, the probe comprises more than 30

nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In other embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom).

Preferably, at least 5 to 10 of these labeled probes are used, and more preferably at least about 20 or 30 are 5 used to provide a unique pattern. The resultant bands appearing from the hybridization of a large sample of extended cDNAs (or genomic DNAs obtainable therefrom) will be a unique identifier. Since the restriction enzyme cleavage will be different for every individual, the band pattern on the Southern blot will also be unique. Increasing the number of extended cDNA probes will provide a statistically higher level of confidence in the identification since there will be an increased number of sets of bands used for identification.

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EXAMPLE 46

Dot Blot Identification Procedure

Another technique for identifying individuals using the extended cDNA sequences disclosed herein utilizes a dot blot hybridization technique.

Genomic DNA is isolated from nuclei of subject to be identified. Oligonucleotide probes of approximately 30 bp 15 in length are synthesized that correspond to at least 10, preferably 50 sequences from the extended cDNAs or genomic DNAs obtainable therefrom. The probes are used to hybridize to the genomic DNA through conditions known to those in the art. The oligonucleotides are end labeled with P32 using polynucleotide kinase (Pharmacia). Dot Blots are created by spotting the genomic DNA onto nitrocellulose or the like using a vacuum dot blot manifold (BioRad, Richmond California). The nitrocellulose filter containing the genomic sequences is baked or UV linked to the filter, prehybridized and 20 hybridized with labeled probe using techniques known in the art (Davis et al. supra). The 32P labeled DNA fragments are sequentially hybridized with successively stringent conditions to detect minimal differences between the 30 bp sequence and the DNA. Tetramethylammonium chloride is useful for identifying clones containing small numbers of nucleotide mismatches (Wood et al., Proc. Natl. Acad. Sci. USA 82(6):1585-1588 (1985)). A unique pattern of dots distinguishes one individual from another individual.

Extended cDNAs or oligonucleotides containing at least 10 consecutive bases from these sequences can be used as probes in the following alternative fingerprinting technique. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). More preferably, the probe comprises at least 20-30 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In some embodiments, the probe comprises more than 30 nucleotides from the extended cDNA (or genomic 30 DNAs obtainable therefrom). In other embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom).

Preferably, a plurality of probes having sequences from different genes are used in the alternative fingerprinting technique. Example 47 below provides a representative alternative fingerprinting procedure in which the probes are derived from extended cDNAs.

EXAMPLE 47

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Alternative "Fingerprint" Identification Technique

20-mer oligonucleotides are prepared from a large number, e.g. 5D, 100, or 200, of extended cDNA sequences (or genomic DNAs obtainable therefrom) using commercially available oligonucleotide services such as Genset, Paris, France. Cell samples from the test subject are processed for DNA using techniques well known to those with skill in the art. The nucleic acid is digested with restriction enzymes such as EcoRI and Xbal. Following digestion, samples are applied to wells for electrophoresis. The procedure, as known in the art, may be modified to accommodate polyacrylamide electrophoresis, however in this example, samples containing 5 ug of DNA are loaded into wells and separated on 0.8% agarose gels. The gels are transferred onto nitrocellulose using standard Southern blotting techniques.

10 ng of each of the oligonucleotides are pooled and end-labeled with P³². The nitrocellulose is prehybridized with blocking solution and hybridized with the labeled probes. Following hybridization and washing, the nitrocellulose filter is exposed to X-Omat AR X-ray film. The resulting hybridization pattern will be unique for each individual.

It is additionally contemplated within this example that the number of probe sequences used can be varied for additional accuracy or clarity.

The antibodies generated in Examples 30 and 40 above may be used to identify the tissue type or cell species 20 from which a sample is derived as described above.

EXAMPLE 48

Identification of Tissue Types or Cell Species by Means of

Labeled Tissue Specific Antibodies

Identification of specific tissues is accomplished by the visualization of tissue specific antigens by means of
antibody preparations according to Examples 30 and 40 which are conjugated, directly or indirectly to a detectable
marker. Selected labeled antibody species bind to their specific antigen binding partner in tissue sections, cell
suspensions, or in extracts of soluble proteins from a tissue sample to provide a pattern for qualitative or semiqualitative interpretation.

Antisera for these procedures must have a potency exceeding that of the native preparation, and for that
reason, antibodies are concentrated to a mg/ml level by isolation of the gamma globulin fraction, for example, by ionexchange chromatography or by ammonium sulfate fractionation. Also, to provide the most specific antisera, unwanted
antibodies, for example to common proteins, must be removed from the gamma globulin fraction, for example by means
of insoluble immunoabsorbents, before the antibodies are labeled with the marker. Either monoclonal or heterologous
antisera is suitable for either procedure.

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A. Immunohistochemical Techniques

Purified, high-titer antibodies, prepared as described above, are conjugated to a detectable marker, as described, for example, by Fudenberg, H., Chap. 26 in: Basic 503 Clinical Immunology, 3rd Ed. Lange, Los Altos, California (1980) or Rose, N. et al., Chap. 12 in: Methods in Immunodiagnosis, 2d Ed. John Wiley 503 Sons, New York (1980).

A fluorescent marker, either fluorescein or rhodamine, is preferred, but antibodies can also be labeled with an enzyme that supports a color producing reaction with a substrate, such as horseradish peroxidase. Markers can be added to tissue-bound antibody in a second step, as described below. Alternatively, the specific antitissue antibodies can be labeled with ferritin or other electron dense particles, and localization of the ferritin coupled antigen antibody complexes achieved by means of an electron microscope. In yet another approach, the antibodies are radiolabeled, with, for example 1251, and detected by overlaying the antibody treated preparation with photographic emulsion.

Preparations to carry out the procedures can comprise monoclonal or polyclonal antibodies to a single protein or peptide identified as specific to a tissue type, for example, brain tissue, or antibody preparations to several antigenically distinct tissue specific antigens can be used in panels, independently or in mixtures, as required.

Tissue sections and cell suspensions are prepared for immunohistochemical examination according to common histological techniques. Multiple cryostat sections (about 4 μ m, unfixed) of the unknown tissue and known control, are mounted and each slide covered with different dilutions of the antibody preparation. Sections of known and unknown tissues should also be treated with preparations to provide a positive control, a negative control, for example, pre-immune sera, and a control for non-specific staining, for example, buffer.

Treated sections are incubated in a humid chamber for 30 min at room temperature, rinsed, then washed in buffer for 30-45 min. Excess fluid is blotted away, and the marker developed.

If the tissue specific antibody was not labeled in the first incubation, it can be labeled at this time in a second antibody-antibody reaction, for example, by adding fluorescein- or enzyme-conjugated antibody against the immunoglobulin class of the antiserum-producing species, for example, fluorescein labeled antibody to mouse IgG. Such labeled sera are commercially available.

The antigen found in the tissues by the above procedure can be quantified by measuring the intensity of color or fluorescence on the tissue section, and calibrating that signal using appropriate standards.

B. Identification of Tissue Specific Soluble Proteins

The visualization of tissue specific proteins and identification of unknown tissues from that procedure is

carried out using the labeled antibody reagents and detection strategy as described for immunohistochemistry; however
the sample is prepared according to an electrophoretic technique to distribute the proteins extracted from the tissue in
an orderly array on the basis of molecular weight for detection.

A tissue sample is homogenized using a Virtis apparatus; cell suspensions are disrupted by Dounce homogenization or osmotic lysis, using detergents in either case as required to disrupt cell membranes, as is the practice

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in the art. Insoluble cell components such as nuclei, microsomes, and membrane fragments are removed by ultracentrifugation, and the soluble protein-containing fraction concentrated if necessary and reserved for analysis.

A sample of the soluble protein solution is resolved into individual protein species by conventional SDS polyacrylamide electrophoresis as described, for example, by Davis, L. et al., Section 19-2 in: Basic Methods in 5 Molecular Biology (P. Leder, ed), Elsevier, New York (1986), using a range of amounts of polyacrylamide in a set of gels to resolve the entire molecular weight range of proteins to be detected in the sample. A size marker is run in parallel for purposes of estimating molecular weights of the constituent proteins. Sample size for analysis is a convenient volume of from 5 to 55 µl, and containing from about 1 to 100 µg protein. An aliquot of each of the resolved proteins is transferred by blotting to a nitrocellulose filter paper, a process that maintains the pattern of resolution. Multiple copies 10 are prepared. The procedure, known as Western Blot Analysis, is well described in Davis, L. et al., (above) Section 19.3. One set of nitrocellulose blots is stained with Coomassie Blue dye to visualize the entire set of proteins for comparison with the antibody bound proteins. The remaining nitrocellulose filters are then incubated with a solution of one or more specific antisera to tissue specific proteins prepared as described in Examples 30 and 40. In this procedure, as in procedure A above, appropriate positive and negative sample and reagent controls are run.

In either procedure A or B, a detectable label can be attached to the primary tissue antigen-primary antibody complex according to various strategies and permutations thereof. In a straightforward approach, the primary specific antibody can be labeled; alternatively, the unlabeled complex can be bound by a labeled secondary anti-IgG antibody. In other approaches, either the primary or secondary antibody is conjugated to a biotin molecule, which can, in a subsequent step, bind an avidin conjugated marker. According to yet another strategy, enzyme labeled or radioactive 20 protein A, which has the property of binding to any IgG, is bound in a final step to either the primary or secondary antibody.

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The visualization of tissue specific antigen binding at levels above those seen in control tissues to one or more tissue specific antibodies, prepared from the gene sequences identified from extended cDNA sequences, can identify tissues of unknown origin, for example, forensic samples, or differentiated tumor tissue that has metastasized to foreign 25 bodily sites.

In addition to their applications in forensics and identification, extended cDNAs (or genomic DNAs obtainable therefrom) may be mapped to their chromosomal locations. Example 49 below describes radiation hybrid (RH) mapping of human chromosomal regions using extended cDNAs. Example 50 below describes a representative procedure for mapping an extended cDNA (or a genomic DNA obtainable therefrom) to its location on a human chromosome. Example 30 51 below describes mapping of extended cDNAs (or genomic DNAs obtainable therefrom) on metaphase chromosomes by Fluorescence In Situ Hybridization (FISH).

EXAMPLE 49

Radiation hybrid mapping of Extended cDNAs to the human genome

Radiation hybrid (RH) mapping is a somatic cell genetic approach that can be used for high resolution mapping of the human genome. In this approach, cell lines containing one or more human chromosomes are lethally irradiated, breaking each chromosome into fragments whose size depends on the radiation dose. These fragments are rescued by fusion with cultured rodent cells, yielding subclones containing different portions of the human genome. This technique is described by Benham et al. (*Genomics* 4:509-517, 1989) and Cox et al., (*Science* 250:245-250, 1990). The random and independent nature of the subclones permits efficient mapping of any human genome marker. Human DNA isolated from a panel of 80-100 cell lines provides a mapping reagent for ordering extended cDNAs (or genomic DNAs obtainable therefrom). In this approach, the frequency of breakage between markers is used to measure distance, allowing construction of fine resolution maps as has been done using conventional ESTs (Schuler et al., *Science* 274:540-546, 1996).

RH mapping has been used to generate a high-resolution whole genome radiation hybrid map of human chromosome 17q22-q25.3 across the genes for growth hormone (GH) and thyr.idine kinase (TK) (Foster et al., *Genomics* 33:185-192, 1996), the region surrounding the Gorlin syndrome gene (Obermayr et al., *Eur. J. Hum. Genet.* 4:242-245, 1996), 60 loci covering the entire short arm of chromosome 12 (Raeymaekers et al., *Genomics* 29:170-178, 1995), the region of human chromosome 22 containing the neurofibromatosis type 2 locus (Frazer et al., *Genomics* 14:574-584, 1992) and 13 loci on the long arm of chromosome 5 (Warrington et al., *Genomics* 11:701-708, 1991).

EXAMPLE 50

Mapping of Extended cDNAs to Human

Chromosomes using PCR techniques

Extended cDNAs (or genomic DNAs obtainable therefrom) may be assigned to human chromosomes using PCR based methodologies. In such approaches, oligonucleotide primer pairs are designed from the extended cDNA sequence (or the sequence of a genomic DNA obtainable therefrom) to minimize the chance of amplifying through an intron. Preferably, the oligonucleotide primers are 18-23 bp in length and are designed for PCR amplification. The creation of PCR primers from known sequences is well known to those with skill in the art. For a review of PCR technology see Erlich, H.A., PCR Technology; Principles and Applications for DNA Amplification. 1992. W.H. Freeman and Co., New York.

The primers are used in polymerase chain reactions (PCR) to amplify templates from total human genomic DNA. PCR conditions are as follows: 60 ng of genomic DNA is used as a template for PCR with 80 ng of each oligonucleotide primer, 0.6 unit of Taq polymerase, and 1 µCu of a ³²P-labeled deoxycytidine triphosphate. The PCR is performed in a microplate thermocycler (Techne) under the following conditions: 30 cycles of 94°C, 1.4 min; 55°C, 2 min; and 72°C, 2 min; with a final extension at 72°C for 10 min. The amplified products are analyzed on a 6% polyacrylamide sequencing gel and visualized by autoradiography. If the length of the resulting PCR product is identical to the distance between the ends of the primer sequences in the extended cDNA from which the primers are derived, then the PCR reaction is repeated with DNA templates from two panels of human-rodent somatic cell hybrids, BIOS

PCRable DNA (BIOS Corporation) and NIGMS Human-Rodent Somatic Cell Hybrid Mapping Panel Number 1 (NIGMS, Camden, NJ).

PCR is used to screen a series of somatic cell hybrid cell lines containing defined sets of human chromosomes for the presence of a given extended cDNA (or genomic DNA obtainable therefrom). DNA is isolated from the somatic hybrids and used as starting templates for PCR reactions using the primer pairs from the extended cDNAs (or genomic DNAs obtainable therefrom). Only those somatic cell hybrids with chromosomes containing the human gene corresponding to the extended cDNA (or genomic DNA obtainable therefrom) will yield an amplified fragment. The extended cDNAs (or genomic DNAs obtainable therefrom) are assigned to a chromosome by analysis of the segregation pattern of PCR products from the somatic hybrid DNA templates. The single human chromosome present in all cell hybrids that give rise to an amplified fragment is the chromosome containing that extended cDNA (or genomic DNA obtainable therefrom). For a review of techniques and analysis of results from somatic cell gene mapping experiments. (See Ledbetter et al., Genomics 6:475-481 (1990).)

Alternatively, the extended cDNAs (or genomic DNAs obtainable therefrom) may be mapped to individual chromosomes using FISH as described in Example 51 below.

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EXAMPLE 51

Mapping of Extended 5' ESTs to Chromosomes

Using Fluorescence in situ Hybridization

Fluorescence in situ hybridization allows the extended cDNA (or genomic DNA obtainable therefrom) to be mapped to a particular location on a given chromosome. The chromosomes to be used for fluorescence in situ hybridization techniques may be obtained from a variety of sources including cell cultures, tissues, or whole blood.

In a preferred embodiment, chromosomal localization of an extended cDNA (or genomic DNA obtainable therefrom) is obtained by FISH as described by Cherif et al. (*Proc. Natl. Acad. Sci. U.S.A.*, 87:6639-6643, 1990).

Metaphase chromosomes are prepared from phytohemagglutinin (PHA)-stimulated blood cell donors. PHA-stimulated lymphocytes from healthy males are cultured for 72 h in RPMI-1640 medium. For synchronization, methotrexate (10 μM) is added for 17 h, followed by addition of 5-bromodeoxyuridine (5-BudR, 0.1 mM) for 6 h. Colcemid (1 μg/ml) is added for the last 15 min before harvesting the cells. Cells are collected, washed in RPMI, incubated with a hypotonic solution of KCI (75 mM) at 37°C for 15 min and fixed in three changes of methanol:acetic acid (3:1). The cell suspension is dropped onto a glass slide and air dried. The extended cDNA (or genomic DNA obtainable therefrom) is labeled with biotin-16 dUTP by nick translation according to the manufacturer's instructions (Bethesda Research

Laboratories, Bethesda, MD), purified using a Sephadex G-50 column (Pharmacia, Upssala, Sweden) and precipitated. Just prior to hybridization, the DNA pellet is dissolved in hybridization buffer (50% formamide, 2 x SSC, 10% dextran sulfate, 1 mg/ml sonicated salmon sperm DNA, pH 7) and the probe is denatured at 70°C for 5-10 min.

Slides kept at $\cdot 20^{\circ}$ C are treated for 1 h at 37°C with RNase A (100 μ g/ml), rinsed three times in 2 X SSC and dehydrated in an ethanol series. Chromosome preparations are denatured in 70% formamide, 2 X SSC for 2 min at

70°C, then dehydrated at 4°C. The slides are treated with proteinase K (10 μg/100 ml in 20 mM Tris·HCl, 2 mM CaCl₂) at 37°C for 8 min and dehydrated. The hybridization mixture containing the probe is placed on the slide, covered with a coverslip, sealed with rubber cement and incubated overnight in a humid chamber at 37°C. After hybridization and post-hybridization washes, the biotinylated probe is detected by avidin-FITC and amplified with additional layers of biotinylated goat anti-avidin and avidin-FITC. For chromosomal localization, fluorescent R-bands are obtained as previously described (Cherif et al., *supra*.). The slides are observed under a LEICA fluorescence microscope (DMRXA). Chromosomes are counterstained with propidium iodide and the fluorescent signal of the probe appears as two symmetrical yellow-green spots on both chromatids of the fluorescent R-band chromosome (red). Thus, a particular extended cDNA (or genomic DNA obtainable therefrom) may be localized to a particular cytogenetic R-band on a given

Once the extended cDNAs (or genomic DNAs obtainable therefrom) have been assigned to particular chromosomes using the techniques described in Examples 49-51 above, they may be utilized to construct a high resolution map of the chromosomes on which they are located or to identify the chromosomes in a sample.

EXAMPLE 52

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Use of Extended cDNAs to Construct or Expand Chromosome Maps

Chromosome mapping involves assigning a given unique sequence to a particular chromosome as described above. Once the unique sequence has been mapped to a given chromosome, it is ordered relative to other unique sequences located on the same chromosome. One approach to chromosome mapping utilizes a series of yeast artificial chromosomes (YACs) bearing several thousand long inserts derived from the chromosomes of the organism from which the extended cDNAs (or genomic DNAs obtainable therefrom) are obtained. This approach is described in Ramaiah Nagaraja et al. Genome Research 7:210-222, March 1997. Briefly, in this approach each chromosome is broken into overlapping pieces which are inserted into the YAC vector. The YAC inserts are screened using PCR or other methods to determine whether they include the extended cDNA (or genomic DNA obtainable therefrom) whose position is to be determined. Once an insert has been found which includes the extended cDNA (or genomic DNA obtainable therefrom), the insert can be analyzed by PCR or other methods to determine whether the insert also contains other sequences known to be on the chromosome or in the region from which the extended cDNA (or genomic DNA obtainable therefrom) was derived. This process can be repeated for each insert in the YAC library to determine the location of each of the extended cDNAs (or genomic DNAs obtainable therefrom) relative to one another and to other known chromosomal markers. In this way, a high resolution map of the distribution of numerous unique markers along each of the organisms 30 chromosomes may be obtained.

As described in Example 53 below extended cDNAs (or genomic DNAs obtainable therefrom) may also be used to identify genes associated with a particular phenotype, such as hereditary disease or drug response.

EXAMPLE 53

Identification of genes associated with hereditary diseases or drug response

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This example illustrates an approach useful for the association of extended cDNAs (or genomic DNAs obtainable therefrom) with particular phenotypic characteristics. In this example, a particular extended cDNA (or genomic DNA obtainable therefrom) is used as a test probe to associate that extended cDNA (or genomic DNA obtainable therefrom) with a particular phenotypic characteristic.

Extended cDNAs (or genomic DNAs obtainable therefrom) are mapped to a particular location on a human chromosome using techniques such as those described in Examples 49 and 50 or other techniques known in the art. A search of Mendelian Inheritance in Man (V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library) reveals the region of the human chromosome which contains the extended cDNA (or genomic DNA obtainable therefrom) to be a very gene rich region containing several known genes and several 10 diseases or phenotypes for which genes have not been identified. The gene corresponding to this extended cDNA (or genomic DNA obtainable therefrom) thus becomes an immediate candidate for each of these genetic diseases.

Cells from patients with these diseases or phenotypes are isolated and expanded in culture. PCR primers from the extended cDNA (or genomic DNA obtainable therefrom) are used to screen genomic DNA, mRNA or cDNA obtained from the patients. Extended cDNAs (or genomic DNAs obtainable therefrom) that are not amplified in the patients can 15 be positively associated with a particular disease by further analysis. Alternatively, the PCR analysis may yield fragments of different lengths when the samples are derived from an individual having the phenotype associated with the disease than when the sample is derived from a healthy individual, indicating that the gene containing the extended cDNA may be responsible for the genetic disease.

VI. Use of Extended cDNAs (or genomic DNAs obtainable therefrom) to Construct Vectors

The present extended cDNAs (or genomic DNAs obtainable therefrom) may also be used to construct secretion vectors capable of directing the secretion of the proteins encoded by genes inserted in the vectors. Such secretion vectors may facilitate the purification or enrichment of the proteins encoded by genes inserted therein by reducing the number of background proteins from which the desired protein must be purified or enriched. Exemplary secretion vectors are described in Example 54 below.

EXAMPLE 54

Construction of Secretion Vectors

The secretion vectors of the present invention include a promoter capable of directing gene expression in the host cell, tissue, or organism of interest. Such promoters include the Rous Sarcoma Virus promoter, the SV40 promoter, the human cytomegalovirus promoter, and other promoters familiar to those skilled in the art.

A signal sequence from an extended cDNA (or genomic DNA obtainable therefrom), such as one of the signal sequences in SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above, is operably linked to the promoter such that the mRNA transcribed from the promoter will direct the translation of the signal peptide. The host cell, tissue, or organism may be any cell, tissue, or organism which recognizes the signal peptide encoded by the signal sequence in the extended cDNA (or genomic DNA obtainable therefrom). Suitable hosts include mammalian cells, tissues or organisms, avian cells, tissues, or organisms, insect cells, tissues or organisms, or yeast.

In addition, the secretion vector contains cloning sites for inserting genes encoding the proteins which are to be secreted. The cloning sites facilitate the cloning of the insert gene in frame with the signal sequence such that a fusion protein in which the signal peptide is fused to the protein encoded by the inserted gene is expressed from the mRNA transcribed from the promoter. The signal peptide directs the extracellular secretion of the fusion protein.

The secretion vector may be DNA or RNA and may integrate into the chromosome of the host, be stably maintained as an extrachromosomal replicon in the host, be an artificial chromosome, or be transiently present in the host. Many nucleic acid backbones suitable for use as secretion vectors are known to those skilled in the art, including retroviral vectors, SV40 vectors, Bovine Papilloma Virus vectors, yeast integrating plasmids, yeast episomal plasmids, yeast artificial chromosomes, human artificial chromosomes, P element vectors, baculovirus vectors, or bacterial plasmids capable of being transiently introduced into the host.

The secretion vector may also contain a polyA signal such that the polyA signal is located downstream of the gene inserted into the secretion vector.

After the gene encoding the protein for which secretion is desired is inserted into the secretion vector, the secretion vector is introduced into the host cell, tissue, or organism using calcium phosphate precipitation, DEAE-Dextran, electroporation, liposome-mediated transfection, viral particles or as naked DNA. The protein encoded by the inserted gene is then purified or enriched from the supernatant using conventional techniques such as ammonium sulfate precipitation, immunoprecipitation, immunochromatography, size exclusion chromatography, ion exchange chromatography, and hplc. Alternatively, the secreted protein may be in a sufficiently enriched or pure state in the supernatant or growth media of the host to permit it to be used for its intended purpose without further enrichment.

The signal sequences may also be inserted into vectors designed for gene therapy. In such vectors, the signal sequence is operably linked to a promoter such that mRNA transcribed from the promoter encodes the signal peptide. A cloning site is located downstream of the signal sequence such that a gene encoding a protein whose secretion is desired may readily be inserted into the vector and fused to the signal sequence. The vector is introduced into an appropriate host cell. The protein expressed from the promoter is secreted extracellularly, thereby producing a therapeutic effect.

The extended cDNAs or 5' ESTs may also be used to clone sequences located upstream of the extended cDNAs or 5' ESTs which are capable of regulating gene expression, including promoter sequences, enhancer sequences, and other upstream sequences which influence transcription or translation levels. Once identified and cloned, these upstream regulatory sequences may be used in expression vectors designed to direct the expression of an inserted gene in a desired spatial, temporal, developmental, or quantitative fashion. Example 55 describes a method for cloning sequences upstream of the extended cDNAs or 5' ESTs.

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Use of Extended cDNAs or 5' ESTs to Clone Upstream

Sequences from Genomic DNA

Sequences derived from extended cDNAs or 5' ESTs may be used to isolate the promoters of the corresponding genes using chromosome walking techniques. In one chromosome walking technique, which utilizes the 5 GenomeWalker™ kit available from Clontech, five complete genomic DNA samples are each digested with a different restriction enzyme which has a 6 base recognition site and leaves a blunt end. Following digestion, oligonucleotide adapters are ligated to each end of the resulting genomic DNA fragments.

For each of the five genomic DNA libraries, a first PCR reaction is performed according to the manufacturer's instructions using an outer adaptor primer provided in the kit and an outer gene specific primer. The gene specific primer 10 should be selected to be specific for the extended cDNA or 5' EST of interest and should have a melting temperature. length, and location in the extended cDNA or ' EST which is consistent with its use in PCR reactions. Each first PCR reaction contains 5ng of genomic DNA, 5 μ l of 10X Tth reaction buffer, 0.2 mM of each dNTP, 0.2 μ M each of outer adaptor primer and outer gene specific primer, 1.1 mM of Mg(OAc), and 1 μ l of the Tth polymerase 50X mix in a total volume of 50 μ l. The reaction cycle for the first PCR reaction is as follows: 1 min @ 94°C / 2 sec @ 94°C, 3 min @ 15 72°C (7 cycles) / 2 sec @ 94°C, 3 min @ 67°C (32 cycles) / 5 min @ 67°C.

The product of the first PCR reaction is diluted and used as a template for a second PCR reaction according to the manufacturer's instructions using a pair of nested primers which are located internally on the amplicon resulting from the first PCR reaction. For example, 5 μ l of the reaction product of the first PCR reaction mixture may be diluted 180 times. Reactions are made in a 50 μ l volume having a composition identical to that of the first PCR reaction except 20 the nested primers are used. The first nested primer is specific for the adaptor, and is provided with the GenomeWalker™ kit. The second nested primer is specific for the particular extended cDNA or 5' EST for which the promoter is to be cloned and should have a melting temperature, length, and location in the extended cDNA or 5' EST which is consistent with its use in PCR reactions. The reaction parameters of the second PCR reaction are as follows: 1 min @ 94°C / 2 sec @ 94°C, 3 min @ 72°C (6 cycles) / 2 sec @ 94°C, 3 min @ 67°C (25 cycles) / 5 min @ 67°C

The product of the second PCR reaction is purified, cloned, and sequenced using standard techniques. Alternatively, two or more human genomic DNA libraries can be constructed by using two or more restriction enzymes. The digested genomic ONA is cloned into vectors which can be converted into single stranded, circular, or linear DNA. A biotinylated oligonucleotide comprising at least 15 nucleotides from the extended cDNA or 5' EST sequence is hybridized to the single stranded DNA. Hybrids between the biotinylated oligonucleotide and the single stranded DNA containing 30 the extended cONA or EST sequence are isolated as described in Example 29 above. Thereafter, the single stranded DNA containing the extended cDNA or EST sequence is released from the beads and converted into double stranded DNA using a primer specific for the extended cDNA or 5' EST sequence or a primer corresponding to a sequence included in the cloning vector. The resulting double stranded DNA is transformed into bacteria. DNAs containing the 5' EST or extended cONA sequences are identified by colony PCR or colony hybridization.

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Once the upstream genomic sequences have been cloned and sequenced as described above, prospective promoters and transcription start sites within the upstream sequences may be identified by comparing the sequences upstream of the extended cDNAs or 5' ESTs with databases containing known transcription start sites, transcription factor binding sites, or promoter sequences.

In addition, promoters in the upstream sequences may be identified using promoter reporter vectors as described in Example 56.

EXAMPLE 56

Identification of Promoters in Cloned Upstream Sequences

The genomic sequences upstream of the extended cDNAs or 5' ESTs are cloned into a suitable promoter 10 reporter vector, such as the pSEAP-Basic, pSEAP-Enhancer, pβgal-Basic, pβgal-Enhancer, or pEGFP-1 Promoter Reporter vectors available from Clontech. Briefly, each of these promoter reporter vectors include multiple cloning sites positioned upstream of a reporter gene encoding a readily assayable protein such as secreted alkaline phosphatase, β galactosidase, or green fluorescent protein. The sequences upstream of the extended cDNAs or 5' ESTs are inserted into the cloning sites upstream of the reporter gene in both orientations and introduced into an appropriate host cell. The 15 level of reporter protein is assayed and compared to the level obtained from a vector which lacks an insert in the cloning site. The presence of an elevated expression level in the vector containing the insert with respect to the control vector indicates the presence of a promoter in the insert. If necessary, the upstream sequences can be cloned into vectors which contain an enhancer for augmenting transcription levels from weak promoter sequences. A significant level of expression above that observed with the vector lacking an insert indicates that a promoter sequence is present in the 20 inserted upstream sequence.

Appropriate host cells for the promoter reporter vectors may be chosen based on the results of the above described determination of expression patterns of the extended cDNAs and ESTs. For example, if the expression pattern analysis indicates that the mRNA corresponding to a particular extended cDNA or 5' EST is expressed in fibroblasts, the promoter reporter vector may be introduced into a human fibroblast cell line.

Promoter sequences within the upstream genomic DNA may be further defined by constructing nested deletions in the upstream DNA using conventional techniques such as Exonuclease III digestion. The resulting deletion fragments can be inserted into the promoter reporter vector to determine whether the deletion has reduced or obliterated promoter activity. In this way, the boundaries of the promoters may be defined. If desired, potential individual regulatory sites within the promoter may be identified using site directed mutagenesis or linker scanning to obliterate 30 potential transcription factor binding sites within the promoter individually or in combination. The effects of these mutations on transcription levels may be determined by inserting the mutations into the cloning sites in the promoter reporter vectors.

EXAMPLE 57

Cloning and Identification of Promoters

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Using the method described in Example 55 above with 5' ESTs, sequences upstream of several genes were obtained. Using the primer pairs GGG AAG ATG GAG ATA GTA TTG CCT G (SEQ ID NO:29) and CTG CCA TGT ACA TGA TAG AGA GAT TC (SEQ ID NO:30), the promoter having the internal designation P13H2 (SEQ ID NO:31) was obtained.

5 Using the primer pairs GTA CCA GGGG ACT GTG ACC ATT GC (SEQ ID NO:32) and CTG TGA CCA TTG CTC CCA AGA GAG (SEQ ID NO:33), the promoter having the internal designation P15B4 (SEQ ID NO:34) was obtained.

Using the primer pairs CTG GGA TGG AAG GCA CGG TA (SEQ ID NO:35) and GAG ACC ACA CAG CTA GAC AA (SEQ ID NO:36), the promoter having the internal designation P29B6 (SEQ ID NO:37) was obtained.

Figure 8 provides a schematic description of the promoters isolated and the way they are assembled with the corresponding 5' tags. The upstream sequences were screened for the presence of motifs resembling transcription factor binding sites or known transcription start sites using the computer program MatInspector release 2.0, August 1996.

Figure 9 describes the transcription factor binding sites present in each of these promoters. The columns labeled matrice provides the name of the MatInspector matrix used. The column labeled position provides the 5' postion of the promoter site. Numeration of the sequence starts from the transcription site as determined by matching the genomic sequence with the 5' EST sequence. The column labeled "orientation" indicates the DNA strand on which the site is found, with the + strand being the coding strand as determined by matching the genomic sequence with the sequence of the 5' EST. The column labeled "score" provides the MatInspector score found for this site. The column labeled "length" provides the length of the site in nucleotides. The column labeled "sequence" provides the sequence of the site found.

The promoters and other regulatory sequences located upstream of the extended cDNAs or 5' ESTs may be used to design expression vectors capable of directing the expression of an inserted gene in a desired spatial, temporal, developmental, or quantitative manner. A promoter capable of directing the desired spatial, temporal, developmental, and quantitative patterns may be selected using the results of the expression analysis described in Example 26 above. For example, if a promoter which confers a high level of expression in muscle is desired, the promoter sequence upstream of an extended cDNA or 5' EST derived from an mRNA which is expressed at a high level in muscle, as determined by the method of Example 26, may be used in the expression vector.

Preferably, the desired promoter is placed near multiple restriction sites to facilitate the cloning of the desired insert downstream of the promoter, such that the promoter is able to drive expression of the inserted gene. The promoter may be inserted in conventional nucleic acid backbones designed for extrachromosomal replication, integration into the host chromosomes or transient expression. Suitable backbones for the present expression vectors include retroviral backbones, backbones from eukaryotic episomes such as SV40 or Bovine Papilloma Virus, backbones from bacterial episomes, or artificial chromosomes.

Preferably, the expression vectors also include a polyA signal downstream of the multiple restriction sites for directing the polyadenylation of mRNA transcribed from the gene inserted into the expression vector.

Following the identification of promoter sequences using the procedures of Examples 55-57, proteins which interact with the promoter may be identified as described in Example 58 below.

EXAMPLE 58

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Identification of Proteins Which Interact with Promoter Sequences, Upstream Regulatory Sequences, or mRNA

Sequences within the promoter region which are likely to bind transcription factors may be identified by homology to known transcription factor binding sites or through conventional mutagenesis or deletion analyses of reporter plasmids containing the promoter sequence. For example, deletions may be made in a reporter plasmid containing the promoter sequence of interest operably linked to an assayable reporter gene. The reporter plasmids carrying various deletions within the promoter region are transfected into an appropriate host cell and the effects of the deletions on expression levels is assessed. Transcription factor binding sites within the regions in which deletions reduce expression levels may be further localized using site directed mutagenesis, linker scanning analysis, or other techniques familiar to those skilled in the art. Nucleic acids encoding proteins which interact with sequences in the promoter may be identified using one-hybrid systems such as those described in the manual accompanying the Matchmaker One-Hybrid System kit avalilabe from Clontech (Catalog No. K1603-1). Briefly, the Matchmaker One-hybrid system is used as follows. The target sequence for which it is desired to identify binding proteins is cloned upstream of a selectable reporter gene and integrated into the yeast genome. Preferably, multiple copies of the target sequences are inserted into the reporter plasmid in tandem.

A library comprised of fusions between cDNAs to be evaluated for the ability to bind to the promoter and the activation domain of a yeast transcription factor, such as GAL4, is transformed into the yeast strain containing the integrated reporter sequence. The yeast are plated on selective media to select cells expressing the selectable marker linked to the promoter sequence. The colonies which grow on the selective media contain genes encoding proteins which bind the target sequence. The inserts in the genes encoding the fusion proteins are further characterized by sequencing. In addition, the inserts may be inserted into expression vectors or in vitro transcription vectors. Binding of the polypeptides encoded by the inserts to the promoter DNA may be confirmed by techniques familiar to those skilled in the art, such as gel shift analysis or DNAse protection analysis.

VII. Use of Extended cDNAs (or Genomic DNAs Obtainable Therefrom) in Gene Therapy

The present invention also comprises the use of extended cDNAs (or genomic DNAs obtainable therefrom) in gene therapy strategies, including antisense and triple helix strategies as described in Examples 57 and 58 below. In antisense approaches, nucleic acid sequences complementary to an mRNA are hybridized to the mRNA intracellularly, thereby blocking the expression of the protein encoded by the mRNA. The antisense sequences may prevent gene expression through a variety of mechanisms. For example, the antisense sequences may inhibit the ability of ribosomes

to translate the mRNA. Alternatively, the antisense sequences may block transport of the mRNA from the nucleus to the cytoplasm, thereby limiting the amount of mRNA available for translation. Another mechanism through which antisense sequences may inhibit gene expression is by interfering with mRNA splicing. In yet another strategy, the antisense nucleic acid may be incorporated in a ribozyme capable of specifically cleaving the target mRNA.

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EXAMPLE 59

Preparation and Use of Antisense Oligonucleotides

The antisense nucleic acid molecules to be used in gene therapy may be either DNA or RNA sequences. They may comprise a sequence complementary to the sequence of the extended cDNA (or genomic DNA obtainable therefrom). The antisense nucleic acids should have a length and melting temperature sufficient to permit formation of an 10 intracellular duplex having sufficient stability to inhibit the expression of the mRNA in the duplex. Strategies for designing antisense nucleic acids suitable for use in gene therapy are disclosed in Green et al., Ann. Rev. Biochem. 55:569-597 (1986) and Izant and Weintraub, Cell 36:1007-1015 (1984).

In some strategies, antisense molecules are obtained from a nucleotide sequence encoding a protein by reversing the orientation of the coding region with respect to a promoter so as to transcribe the opposite strand from 15 that which is normally transcribed in the cell. The antisense molecules may be transcribed using in vitro transcription systems such as those which employ T7 or SP6 polymerase to generate the transcript. Another approach involves transcription of the antisense nucleic acids in vivo by operably linking DNA containing the antisense sequence to a promoter in an expression vector.

Alternatively, oligonucleotides which are complementary to the strand normally transcribed in the cell may be 20 synthesized in vitro. Thus, the antisense nucleic acids are complementary to the corresponding mRNA and are capable of hybridizing to the mRNA to create a duplex. In some embodiments, the antisense sequences may contain modified sugar phosphate backbones to increase stability and make them less sensitive to RNase activity. Examples of modifications suitable for use in antisense strategies are described by Rossi et al., Pharmacol. Ther. 50(2):245-254, (1991).

Various types of antisense oligonucleotides complementary to the sequence of the extended cDNA (or genomic DNA obtainable therefrom) may be used. In one preferred embodiment, stable and semi-stable antisense oligonucleotides described in International Application No. PCT W094/23026 are used. In these moleucles, the 3' end or both the 3' and 5' ends are engaged in intramolecular hydrogen bonding between complementary base pairs. These molecules are better able to withstand exonuclease attacks and exhibit increased stability compared to conventional antisense 30 oligonucleotides.

In another preferred embodiment, the antisense oligodeoxynucleotides against herpes simplex virus types 1 and 2 described in International Application No. WO 95/04141.

In yet another preferred embodiment, the covalently cross-linked antisense oligonucleotides described in International Application No. WO 96/31523 are used. These double- or single-stranded oligonucleotides comprise one or 15

more, respectively, inter- or intra-oligonucleotide covalent cross-linkages, wherein the linkage consists of an amide bond between a primary amine group of one strand and a carboxyl group of the other strand or of the same strand, respectively, the primary amine group being directly substituted in the 2' position of the strand nucleotide monosaccharide ring, and the carboxyl group being carried by an aliphatic spacer group substituted on a nucleotide or nucleotide analog of the other strand or the same strand, respectively.

The antisense oligodeoxynucleotides and oligonucleotides disclosed in International Application No. WO 92/18522 may also be used. These molecules are stable to degradation and contain at least one transcription control recognition sequence which binds to control proteins and are effective as decoys therefor. These molecules may contain "hairpin" structures, "dumbbell" structures, "modified dumbbell" structures, "cross-linked" decoy structures and "loop" structures.

In another preferred embodiment, the cyclic double-stranded oligonucleotides described in European Patent Application No. 0 572 287 A2 are used. These ligated oligonucleotide "dumbbells" contain the binding site for a transcription factor and inhibit expression of the gene under control of the transcription factor by sequestering the factor.

Use of the closed antisense oligonucleotides disclosed in International Application No. WO 92/19732 is also contemplated. Because these molecules have no free ends, they are more resistant to degradation by exonucleases than are conventional oligonucleotides. These oligonucleotides may be multifunctional, interacting with several regions which are not adjacent to the target mRNA.

The appropriate level of antisense nucleic acids required to inhibit gene expression may be determined using in vitro expression analysis. The antisense molecule may be introduced into the cells by diffusion, injection, infection or transfection using procedures known in the art. For example, the antisense nucleic acids can be introduced into the body as a bare or naked oligonucleotide, oligonucleotide encapsulated in lipid, oligonucleotide sequence encapsidated by viral protein, or as an oligonucleotide operably linked to a promoter contained in an expression vector. The expression vector may be any of a variety of expression vectors known in the art, including retroviral or viral vectors, vectors capable of extrachromosomal replication, or integrating vectors. The vectors may be DNA or RNA.

The antisense molecules are introduced onto cell samples at a number of different concentrations preferably between 1x10⁻¹⁰M to 1x10⁻⁴M. Once the minimum concentration that can adequately control gene expression is identified, the optimized dose is translated into a dosage suitable for use in vivo. For example, an inhibiting concentration in culture of 1x10⁻⁷ translates into a dose of approximately 0.6 mg/kg bodyweight. Levels of oligonucleotide approaching 100 mg/kg bodyweight or higher may be possible after testing the toxicity of the oligonucleotide in laboratory animals. It is additionally contemplated that cells from the vertebrate are removed, treated with the antisense oligonucleotide, and reintroduced into the vertebrate.

It is further contemplated that the antisense oligonucleotide sequence is incorporated into a ribozyme sequence to enable the antisense to specifically bind and cleave its target mRNA. For technical applications of ribozyme and antisense oligonucleotides see Rossi et al., supra.

In a preferred application of this invention, the polypeptide encoded by the gene is first identified, so that the 5 effectiveness of antisense inhibition on translation can be monitored using techniques that include but are not limited to antibody-mediated tests such as RIAs and ELISA, functional assays, or radiolabeling.

The extended cDNAs of the present invention (or genomic DNAs obtainable therefrom) may also be used in gene therapy approaches based on intracellular triple helix formation. Triple helix oligonucleotides are used to inhibit transcription from a genome. They are particularly useful for studying alterations in cell activity as it is associated with 10 a particular gene. The extended cDNAs (or genomic DNAs obtainable therefrom) of the present invention or, more preferably, a portion of those sequences, can be used to inhibit gene expression in individuals having diseases associated with expression of a particular gene. Similarly, a portion of the extended cDNA (or genomic DNA obtainable therefrom) can be used to study the effect of inhibiting transcription of a particular gene within a cell. Traditionally, homopurine sequences were considered the most useful for triple helix strategies. However, homopyrimidine sequences can also 15 inhibit gene expression. Such homopyrimidine oligonucleotides bind to the major groove at homopurine:homopyrimidine sequences. Thus, both types of sequences from the extended cDNA or from the gene corresponding to the extended cDNA are contemplated within the scope of this invention.

EXAMPLE 60

Preparation and use of Triple Helix Probes

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The sequences of the extended cDNAs (or genomic DNAs obtainable therefrom) are scanned to identify 10-mer to 20-mer homopyrimidine or homopurine stretches which could be used in triple-helix based strategies for inhibiting gene expression. Following identification of candidate homopyrimidine or homopurine stretches, their efficiency in inhibiting gene expression is assessed by introducing varying amounts of oligonucleotides containing the candidate sequences into tissue culture cells which normally express the target gene. The oligonucleotides may be prepared on an oligonucleotide 25 synthesizer or they may be purchased commercially from a company specializing in custom oligonucleotide synthesis, such as GENSET, Paris, France.

The oligonucleotides may be introduced into the cells using a variety of methods known to those skilled in the art, including but not limited to calcium phosphate precipitation, DEAE-Dextran, electroporation, liposome-mediated transfection or native uptake.

30 Treated cells are monitored for altered cell function or reduced gene expression using techniques such as Northern blotting, RNase protection assays, or PCR based strategies to monitor the transcription levels of the target gene in cells which have been treated with the oligonucleotide . The cell functions to be monitored are predicted based upon the homologies of the target gene corresponding to the extended cDNA from which the oligonucleotide was derived with known gene sequences that have been associated with a particular function. The cell functions can also be

predicted based on the presence of abnormal physiologies within cells derived from individuals with a particular inherited disease, particularly when the extended cDNA is associated with the disease using techniques described in Example 53.

The oligonucleotides which are effective in inhibiting gene expression in tissue culture cells may then be introduced in vivo using the techniques described above and in Example 59 at a dosage calculated based on the in vitro results, as described in Example 59.

In some embodiments, the natural (beta) anomers of the oligonucleotide units can be replaced with alpha anomers to render the oligonucleotide more resistant to nucleases. Further, an intercalating agent such as ethidium bromide, or the like, can be attached to the 3' end of the alpha oligonucleotide to stabilize the triple helix. For information on the generation of oligonucleotides suitable for triple helix formation see Griffin et al. (Science 245:967-10 971 (1989).

EXAMPLE 61

Use of Extended cDNAs to Express an Encoded Protein in a Host Organism

The extended cDNAs of the present invention may also be used to express an encoded protein in a host organism to produce a beneficial effect. In such procedures, the encoded protein may be transiently expressed in the host organism or stably expressed in the host organism. The encoded protein may have any of the activities described above. The encoded protein may be a protein which the host organism lacks or, alternatively, the encoded protein may augment the existing levels of the protein in the host organism.

A full length extended cDNA encoding the signal peptide and the mature protein, or an extended cDNA encoding only the mature protein is introduced into the host organism. The extended cDNA may be introduced into the host organism using a variety of techniques known to those of skill in the art. For example, the extended cDNA may be injected into the host organism as naked DNA such that the encoded protein is expressed in the host organism, thereby producing a beneficial effect.

Alternatively, the extended cDNA may be cloned into an expression vector downstream of a promoter which is active in the host organism. The expression vector may be any of the expression vectors designed for use in gene therapy, including viral or retroviral vectors.

The expression vector may be directly introduced into the host organism such that the encoded protein is expressed in the host organism to produce a beneficial effect. In another approach, the expression vector may be introduced into cells in vitro. Cells containing the expression vector are thereafter selected and introduced into the host organism, where they express the encoded protein to produce a beneficial effect.

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EXAMPLE 62

Use Of Signal Peptides Encoded By 5' Ests Or Sequences

Obtained Therefrom To Import Proteins Into Cells

The short core hydrophobic region (h) of signal peptides encoded by the 5'ESTS or extended cDNAs derived from the 5'ESTs of the present invention may also be used as a carrier to import a peptide or a protein of interest, so-

called cargo, into tissue culture cells (Lin et al., J. Biol. Chem., 270: 14225-14258 (1995); Du et al., J. Peptide Res., 51: 235-243 (1998); Rojas et al., Nature Biotech., 16: 370-375 (1998)).

When cell permeable peptides of limited size (approximately up to 25 amino acids) are to be translocated across cell membrane, chemical synthesis may be used in order to add the h region to either the C-terminus or the N-terminus to the cargo peptide of interest. Alternatively, when longer peptides or proteins are to be imported into cells, nucleic acids can be genetically engineered, using techniques familiar to those skilled in the art, in order to link the extended cDNA sequence encoding the h region to the 5' or the 3' end of a DNA sequence coding for a cargo polypeptide. Such genetically engineered nucleic acids are then translated either *in vitro* or *in vivo* after transfection into appropriate cells, using conventional techniques to produce the resulting cell permeable polypeptide. Suitable hosts cells are then simply incubated with the cell permeable polypeptide which is then translocated across the membrane.

This method may be applied to study diverse intracellular functions and cellular processes. For instance, it has been used to probe functionally relevant domains of intracellular proteins and to examine protein protein interactions involved in signal transduction pathways (Lin et al., supra; Lin et al., J. Biol. Chem., 271: 5305-5308 (1996); Rojas et al., J. Biol. Chem., 271: 27456-27461 (1996); Liu et al., Proc. Natl. Acad. Sci. USA, 93: 11819-11824 (1996); Rojas et al., Bioch. Biophys. Res. Commun., 234: 675-680 (1997)).

Such techniques may be used in cellular therapy to import proteins producing therapeutic effects. For instance, cells isolated from a patient may be treated with imported therapeutic proteins and then re-introduced into the host organism.

Alternatively, the h region of signal peptides of the present invention could be used in combination with a

20 nuclear localization signal to deliver nucleic acids into cell nucleus. Such oligonucleotides may be antisense
oligonucleotides or oligonucleotides designed to form triple helixes, as described in examples 59 and 60 respectively, in
order to inhibit processing and maturation of a target cellular RNA.

EXAMPLE 63

Reassembling & Resequencing of Clones

Full length cDNA clones obtained by the procedure described in Example 27 were double sequenced. These sequences were assembled and the resulting consensus sequences were then reanalyzed. Open reading frames were reassigned following essentially the same process as the one described in Example 27.

After this reanalysis process a few abnormalities were revealed. The sequences presented in SEQ ID NOs: 47, 73, 79, 89, 91, 96, 126, 128, 134, and 139 are apparently unlikely to be genuine full length cDNAs. These clones are missing a stop codon and are thus more probably 3' truncated cDNA sequences. Similarly, the sequences presented in SEQ ID NOs: 45, 50, 54, 57, 73, 74, 89, 92, 95, 98, 126, 129, 130, 131 and 139 may also not be genuine full length cDNAs based on homology studies with existing protein sequences. Although both of these sequences encode a potential start methionine each could represent a 5' truncated cDNA.

In addition, SEQ ID NO: 115 was found to be an alternatively spliced transcript and the identities of some of the bases in SEQ ID NO: 131 were corrected.

Finally, after the reassignment of open reading frames for the clones, new open reading frames were chosen in some instances. For example, in the case of SEQ ID NOs: 41, 47, 50, 52, 54-56, 58, 59, 61, 74, 75, 79, 84, 89, 91, 92, 96, 98, 103, 105, 106, 126, 129, 131, and 133 the new open reading frames were no longer predicted to contain a signal peptide.

As discussed above, Table IV provides the sequence identification numbers of the extended cDNAs of the present invention, the locations of the full coding sequences in SEQ ID NOs: 40-140 and 242-377 (i.e. the nucleotides encoding both the signal peptide and the mature protein, listed under the heading FCS location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the signal peptides (listed under the heading SigPep Location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the mature proteins generated by cleavage of the signal peptides (listed under the heading Mature Polypeptide Location in Table IV), the locations in SEQ ID NOs: 40-140 and 242-377 of stop codons (listed under the heading Stop Codon Location in Table IV) the locations in SEQ ID NOs: 40-140 and 242-377 of polyA signals (listed under the heading 9 PolyA Signal Location in Table IV) and the locations of polyA sites (listed under the heading PolyA Site Location in Table IV).

As discussed above, Table V lists the sequence identification numbers of the polypeptides of SEQ ID NOs: 141-241 and 378-513, the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the full length polypeptide (second column), the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the signal peptides (third column), and the locations of the amino acid residues of SEQ ID NOs: 141-241 and 379-513 in the mature polypeptide created by cleaving the signal peptide from the fall length polypeptide (fourth column). In Table V, and in the appended sequence listing, the first amino acid of the mature protein resulting from cleavage of the signal peptide is designated as amino acid number 1 and the first amino acid of the signal peptide is designated with the appropriate negative number, in accordance with the regulations governing sequence listings.

25

EXAMPLE 64

<u>Functional Analysis of Predicted Protein Sequences</u>

Following double-sequencing, new contigs were assembled for each of the extended cDNAs of the present invention and each was compared to known sequences available at the time of filing. These sequences originate from the following databases: Genbank (release 108 and daily releases up to October, 15, 1998), Genseq (release 32) PIR (release 30 53) and SwissProt (release 35). The predicted proteins of the present invention matching known proteins were further classified into 3 categories depending on the level of homology.

The first category contains proteins of the present invention exhibiting more than 70% identical amino acid residues on the whole length of the matched protein. They are clearly close homologues which most probably have the same function or a very similar function as the matched protein.

The second category contains proteins of the present invention exhibiting more remote homologies (40 to 70% over the whole protein) indicating that the protein of the present inventionmay have functions similar to those of the homologous protein.

The third category contains proteins exhibiting homology (90 to 100%) to a domain of a known protein indicating that the matched protein and the protein of the invention may share similar features.

It should be noted that the numbering of amino acids in the protein sequences discussed in Figures 10 to 15, and Table VIII, the first methionine encountered is designated as amino acid number 1. In the appended sequence listing, the first amino acid of the mature protein resulting from cleavage of the signal peptide is designated as amino acid number 1, and the first amino acid of the signal peptide is designated with the appropriate negative number, in accordance with the regulations governing sequence listings.

In addition all of the corrected amino acid sequences (SEQ ED NOs: 141-241 and 378-513) were scanned for the presence of known protein signatures and motifs. This search was performed against the Prosite 15.0 database, using the Proscan software from the GCG package. Functional signatures and their locations are indicated in Table VIII.

15 A) Proteins which are closely related to known proteins

Protein of SEQ ID NO: 217

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The protein of SEQ ID NO: 217 encoded by the extended cDNA SEQ ID NO: 116 isolated from lymphocyte shows complete identity to a human protein TFAR19 that may play a role in apoptosis (Genbank accession number AF014955, SEQ ID NO: 516) as shown by the alignment in figure 10.

Taken together, these data suggest that the protein of SEQ ID NO: 217 may be involved in the control of development and homeostasis. Thus, this protein may be useful in diagnosis and/or treating several types of disorders including, but not limited to, cancer, autoimmune disorders, viral infections such as AIDS, neurodegenerative disorders, osteoporosis.

25 Proteins of SEO ID NOs: 174, 175 and 232

The proteins of SEQ ID NOs: 174, 175 and 232 encoded by the extended cDNAs SEQ ID NOs:. 73, 74 and 131 respectively and isolated from lymphocytes shows complete extensive homologies to a human secreted protein (Genseq accession number W36955, SEQ ID NO: 517). As shown by the alignments of figure 11, the amino acid residues are identical to those of the 110 amino acid long matched protein except for positions 51 and 108-110 of the matched protein for the protein of SEQ ID NOs: 174, for positions 48, 94 and 108-110 of the matched protein of SEQ ID NOs: 175 and for positions 94, and 108-110 of the matched protein for the protein of SEQ ID NOs: 232. Proteins of SEQ IO NOs: 174 and 232 may represent alternative forms issued from alternative use of polyadenylation signals.

Taken together, these data suggest that the proteins of SEQ ID NOs: 174, 175 and 232 may play a role in cell proliferation and/or differentiation, in immune responses and/or in haematopoeisis. Thus, this protein or part therein,

may be useful in diagnosing and treating several disorders including, but not limited to, cancer, immunological, haematological and/or inflammatory disorders. It may also be useful in modulating the immune and inflammatory responses to infectious agents and/or to suppress graft rejection.

5 Proteins of SEQ ID NO: 231

The protein of SEQ ID NO: 231 encoded by the extended cDNA SEQ ID NO: 130 shows extensive homology with the human E25 protein (Genbank accession number AFO38953, SEQ ID NO: 515). As shown by the alignments in figure 12, the amino acid residues are identical except for position 159 in the 263 amino acid long matched sequence. The matched protein might be involved in the development and differentiation of haematopoietic stem/progenitor cells.

10 In addition, it is the human homologue of a murine protein thought to be involved in chondro-osteogenic differentiation and belonging to a novel multigene family of integral membrane proteins (Deleersnijder et al, J. Biol. Chem., 271: 19475-19482 (1996)).

The protein of invention contains two short segments from positions 1 to 21 and from 100 to 120 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10:685-686 (1994)). The first transmembrane domains matches exactly those predicted for the murine E25 protein.

Taken together, these data suggest that the protein of SEQ ID NO: 231 may be involved in cellular proliferation and differentiation. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer and embryogenesis disorders.

20 Protein of SEQ ID NO: 196

The protein of SEQ ID NO: 196 encoded by the extended cDNA SEQ ID NO: 95 shows extensive homology with the human seventransmembrane protein (Genbank accession number Y11395, SEQ ID NO: 518) and its murine homologue (Genbank accession number Y11550). As shown by the alignments in figure 13, the amino acid residues are identical except for position 174 in the 399 amino acid long human matched sequence. The matched protein potentially associated to stomatin may act as a G-protein coupled receptor and is likely to be important for the signal transduction in neurons and haematopoietic cells (Mayer et al, Biochem. Biophys. Acta., 1395: 301-308 (1998)).

Taken together, these data suggest that the protein of SEQ ID NOs: 196 may be involved in signal transduction. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases cardiovascular disorders, hypertension, renal injury and repair and septic shock.

Protein of SEQ ID NO: 158

The protein of SEQ IO NOs: 158 encoded by the extended cDNA SEQ ID NO: 57 shows homology with the murine subunit 7a of the COP9 complex (Genbank accession number AF071316, SEQ ID NO: 520). As shown by the

alignments in figure 14, the amino acid residues are identical except for positions 90, 172 and 247 in the 275 amino acid long matched sequence. This complex is highly conserved between mammals and higher plants where it has been shown to act as a repressor of photomorphogenesis All the components of the mammalian COP9 complex contain structural features also present in components of the proteasome regulatory complex and the translation initiation complex eIF3 complex, suggesting that the mammalian COP9 complex is an important cellular regulator modulating multiple signaling pathways (Wei et al, Curr. Biol., 8: 919-922 (1998)).

Taken together, these data suggest that the protein of SEQ ID NO: 158 may be involved in cellular signaling, probably as a subunit of the human COP9 complex. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, cardiovascular disorders, hypertension, renal injury and repair and septic shock.

Protein of SEQ ID NO: 226

The protein of SEQ ID NO: 226 encoded by the extended cDNA SEQ ID NO: 125 shows homology with the bovine subunit B14.5B of the NADH-ubiquinone oxidureductase complex (Arizmendi *et al., FEBS Lett.*, 313: 80-84 (1992) and Swissprot accession -number Q02827, SEQ ID NO: 514). As shown by the alignments in figure 15, the amino acid residues are identical except for positions 3-4, 6-12, 32-34, 47, 53-55, 67 and 69-74 in the 120 amino acid long matched sequence. This complex is the first of four complexes located in the inner mitochondrial membrane and composing the mitochondrial electron transport chain. Complex I is involved in the dehydrogenation of NAOH and the transportation of electrons to coenzyme Q. It is composed of 7 subunits encoded by the mitochondrial genome and 34 subunits encoded by the nuclear genome. It is also thought to play a role in the regulation of apoptosis and necrosis. Mitochondriocytopathies due to complex I deficiency are frequently encountered and affect tissues with a high energy demand such as brain (mental retardation, convulsions, movement disorders), heart (cardiomyopathy, conduction disorders), kidney (Fanconi syndrome), skeletal muscle (exercise intolerance, muscle weakness, hypotonia) and/or eye (opthmaloplegia, ptosis, cataract and retinopathy). For a review on complex I see Smeitink *et al., Hum. Mol. Gent.*, 7: 1573-1579 (1998).

Taken together, these data suggest that the protein of SEO ID NO: 226 may be part of the mitochondrial energy-generating system, probably as a subunit of the NADH-ubiquinone oxidoreductase complex. Thus, this protein or part therein, may be useful in diagnosing and/or treating several disorders including, but not limited to, brain disorders (mental retardation, convulsions, movement disorders), 'heart disorders (cardiomyopathy, conduction disorders), kidney, disorders (Fanconi syndrome), skeletal muscle disorders (exercise intolerance, muscle weakness, hypotonia) and/or eye disorders opthmalmoplegia, ptosis, cataract and retinopathy).

B) Proteins which are remotely related to proteins with known functions

Proteins of SEO ID NOs: 149, 150 and 211

The proteins of SEO ID NOs: 1.49,150 and 211 encoded by the extended cDNAs SEO ID NOs: 48, 49 and 110 respectively and found in, skeletal muscle shows homologies with T1/ST2 ligand polypeptide of either human (Genbank accession number U41804 and Genseq accession number W09639) or rodent species (Genbank accession number U41805 and Genseq accession number W09640). These polypeptides are thought to be cytokines that bind to the ST2 receptor, a member of the immunoglobulin family homologous to the interleukin-1 receptor and present on some lymphoma cells. They are predicted to be cell-surface proteins containing a short transmembrane domain. (Gayle et al, J. Biol. Chem., 271: 5784-5789 (1996)). Proteins of SEO ID NOs: 149, 150 and 211 may represent alternative forms issued from alternative use of polyadenylation signals.

The protein of invention contains two short transmembrane segments from positions 5 to 25 and from 195 to 215 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10:685-686 (1994)). The second transmembrane domain matches exactly those of the matched cell-surface protein.

Taken together, these data suggest that the protein of SEQ ID NOs: 149, 150 and 211 may act as a cytokine, thus may play a role in the regulation of cell growth and differentiation and/or in the regulation of the immune response. Thus, this protein or part therein, may be useful in diagnosing and treating several disorders including, but not limited to, cancer, immunological, haematological and/or inflammatory disorders. It may also be useful in modulating the immune and inflammatory responses to infectious agents such as HIV and/or to suppress graft rejection.

Protein of SEQ ID NO: 177

The protein SEQ ID NO: 177 found in testis encoded by the extended cDNA SEQ ID NO: 76 shows homologies to serine protease inhibitor proteins belonging to the pancreatic trypsin inhibitor family (Kunitz) such as the extracellular proteinase inhibitor named chelonianin (Swissprot accession number P00993). The characteristic PROSITE signature of this family is conserved in the protein of the invention (positions 69 to 87) except for a drastic change of the last cysteine residue into an arginine residue.

Taken together, these data suggest that the protein of SEQ ID NO: 177 may be a protease inhibitor, probably
of the Kunitz family. Thus, this protein or part therein, may be useful in diagnosing and treating several disorders including but not limited to, cancer and neurodegenerative disorders such as Alzheimer's disease.

Protein of SEQ ID NO: 146

The protein SEQ ID NO: 146 encoded by the extended cDNA SEQ ID NO: 45 shows homology to human apolipoprotein L (Genbank accession number AF019225). The matched protein is a secreted high density lipoprotein associated with apoA-I-containing lipoproteins which play a key role in reverse cholesterol transport.

Taken together, these data suggest that the protein of SEQ ID NO. 146 may play a role in lipid metabolism. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to,

hyperlipidemia, hypercholesterolemia, atherosclerosis, cardiovascular disorders such as, coronary heart disease, and neurodegenerative disorders such as Alzheimer's disease or dementia.

Protein of SEQ ID NO: 163

The protein SEQ ED NO: 163 encoded by the extended cDNA SEQ ID NO: 62 shows homology to the yeast autophagocytosis protein AUT1 (SwissProt accession number P40344). The matched protein is required for starvation-induced non-specific bulk transport of cytoplasmic proteins to the vacuole.

Taken together, these data suggest that the protein of SEQ ID NO: 163 may play a role in protein transport.

Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to,
autoimmune disorders and immune disorders due to dysfunction of antigen presentation.

C) Proteins homologous to a domain of a protein with known function

Protein of SEQ ID NO: 214

The protein of SEQ ID NO: 214 encoded by the extended cDNA SEQ ID NO: 113 and expressed in adult brain shows extensive homology to part of the murine SHYC protein (Genbank accession number AF072697) which is expressed in the developing and embryonic nervous system as well as along the olfactory pathway in adult brains (Köster et al., Neuroscience Letters., 252: 69-71 (1998)).

Taken together, these data suggest that the protein of SEQ ID NO: 214 may play a role in nervous system development and function. Thus, this protein may be useful in diagnosing and/or treating cancer and/or brain disorders, including neurodegenerative disorders such as Alzheimer's and Parkinson's diseases.

Protein of SEQ ID NO: 225

The protein of SEQ ID NO: 225 encoded by the extended cDNA SEQ ID NO: 124 and expressed in adult prostate belong to the phosphatidylethanolainin-binding protein from which it exhibits the characteristic PROSITE signature from positions 90 to 112 (see table VIII). Proteins from this widespread family, from nematodes to fly, yeast, rodent and primate species, bind hydrophobic ligands such as phospholipids and nucleotides. They are mostly expressed in brain and in testis and are thought to play a role in cell growth and/or maturation, in regulation of the sperm maturation, motility and 'in membrane remodeling. They may act either through signal transduction or through oxidoreduction reactions (for a review see Schoentgen and Jollès, FEBS Letters, 369 : 22-26 (1995)).

Taken together, these data suggest that the protein of SEQ ID NO: 225 may play a role in cell. Thus, these growth, maturation and in membrane remodeling and/or may be related to male fertility. Thus, this protein may be useful in diagnosing and/or treating cancer, neurodegenerative diseases, and/of, disorders related to male fertility and sterility.

Protein of SEQ ID NO: 153

The protein of SEQ ID NO: 153 encoded by the extended cDNA SEQ ID NO. 52 and expressed in brain exhibits homology to different integral membrane proteins. These membrane proteins include the nematode protein SRE-2 (Swissprot accession number Q09273) that belongs to the multigene SRE family of *C. elegans* receptor-like proteins and a family of tricarboxylate carriers conserved between flies and mammals. One member of this matched family is the rat tricarboxylate carrier (Genbank accession number S70011), an anion transporter localized in the inner membrane of mitochondria and involved in the biosynthesis of fatty acids and cholesterol. The protein of the invention contains a short transmembrane segments from positions 5 to 25 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10:685-686 (1994)).

Taken together, these data suggest that the protein of SEQ ID NO: 153 may play a role in signal transduction
and/or in molecule transport. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, immune disorders, cardiovascular disorders, hypertension, renal injury and repair and septic shock

Protein of SEQ ID NO: 213

The protein of SEQ ID NO: 213 encoded by the extended cDNA SEQ ID NO: 112 and expressed in brain exhibits homology with part of the tRNA pseudouridine 55 synthase found in *Escherichia Coli* (Swissprot accession number P09171). This bacterial protein belongs to the NAP57/CBF5/TRUB family of nucleolar proteins found in bacteria, yeasts and mammals involved in rRNA or tRNA biosynthesis, ribosomal subunit assembly and/or centromere/mircotubule binding.

Taken together, these data suggest that the protein of SEQ ID NO: 213 may play a role in rRNA or tRNA biogensis and function. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, hearing loss or disorders linked to chromosomal instability such as dyskeratosis.

Protein of SEQ ED NO: 240

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The protein of SEQ ID NO: 240 encoded by the extended cDNA SEQ ID NO: 139 and expressed in brain exhibits homology with a family of eukaryotic cell surface antigens containing 4 transmembrane domains. The PROSITE signature for this family is conserved in the protein of the invention except for a substitution of an alanine residue in place of any of the following hydrophic residues: leucine, valine, isoleucine or methionine (positions 21 to 36).

The protein of the invention contains three short transmembrane segments from positions 6 to 26, 32 to 52 and from 56 to 76 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10: 685-686 (1994)). These transmembrane domains match the last three transmembrane domains of the matched protein family.

Taken together, these data suggest that the protein of SEQ IO NO: 240 may play a role in immunological and/or inflammatory responses, probably as a cell surface antigen. Thus, this protein or part therein, may be useful in diagnosing and treating several disorders including, but not limited to, cancer, immunological, haematological and/or

inflammatory disorders. It may also be useful in modulating the immune and inflammatory responses to infectious agents and/or to suppress graft rejection.

Protein of SEQ ID NO: 239

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The protein of SEQ ID NO: 239 encoded by the extended cDNA SEQ ID NO: 138 exhibits homology with a conserved region in a family of NA+/H+ exchanger conserved in yeast, nematode and mammals. These cation/proton exchangers are integral membrane proteins with 5 transmembrane segments involved in intracellular pH regulation, maintenance of cell volume, reabsorption of sodium across specialized epithelia, vectorial transport and are also thought to play a role in signal transduction and especially in the induction of cell proliferation and in the induction of apoptosis.

The protein of invention contains four short transmembrane segments from positions 21 to 41, 48 to 68 and from 131 to 151 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10: 685-686 (1994)). The third and fourth transmembrane domains match the fourth and fifth transmembrane segments of the matched family of proteins.

Taken together, these data suggest that the protein of SEQ ID NO: 239 may play a role in membrane

15 permeability and/or in signal transduction. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, cardiovascular disorders, hypertension, renal injury and repair, septic shock as well as disorders of membrane permeability such as diarrhea.

Protein of SEQ ID NO: 200

The protein of SEQ ID NO: 200 encoded by the extended cDNA SEQ ED NO: 99 and expressed in brain exhibits extensive homology to the N-terminus of cell division cycle protein 23 (Genbank accession number AF053977) and also to a lesser extent to its homologue in Saccharomyces cerevisiae. The matched protein is required for chromosome segregation and is part of the anaphae-promoting complex necessary for cell cycle progression to mitosis.

Taken together, these data suggest that the protein of SEQ ID NO: 200 may play a role in cellular mitosis.

Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer and leukemia.

Protein of SEQ ID NO: 230

The protein of SEQ ID NO: 230 encoded by the extended cDNA SEQ ID NO: 129 exhibits extensive homology to the C-terminus of the eta subunit of T-complex polypeptide 1 conserved from yeasts to mammals, and even complete identity with the last 54 amino acid residues of the human protein (Genbank accession number AF026292). The matched protein is a chaperonin which assists the folding of actins and tubulins in eukaryotic cells upon ATP hydrolysis.

Taken together, these data suggest that the protein of SEQ ID NO: 230 may play a role in the folding, transport, assembly and degradation of proteins. Thus, this protein may be useful in diagnosing and/or treating several

types of disorders including, but not limited to, cancer, cardiovascular disorders, immune disorders, neurodegenerative disorders, osteoporosis and arthritis.

Protein of SEQ ED NO: 167

The protein of SEQ ID NO: 167 encoded by the extended cDNA SEQ ID NO: 66 exhibits homology to a monkey pepsinogen A-4 precursor (Swissprot accession number P27678) and to related members of the aspartyl protease family. The matched protein belongs to a family of widely distributed proteolytic enzymes known to exist in vertebrate, fungi, plants, retroviruses and some plant viruses.

Taken together, these data suggest that the protein of SEQ ID NO: 167 may play a role in the degradation of proteins. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, autoimmune disorders and immune disorders due to dysfunction of antigen presentation.

Protein of SEO ID NO: 179

The protein of SEQ ID NO: 179 encoded by the extended cDNA SEQ ID NO: 78 found in testis exhibits

15 homology to part of mammalian colipase precursors. Colipases are secreted cofactors for pancreatic lipases that allow the lipase to anchor at the water-lipid interface. Colipase plays a crucial role in the intestinal digestion and absorption of dietary fats. The 5 cysteines characteristic for this protein family are conserved in the protein of the invention although the colipase PROSITE signature is not.

Taken together, these data suggest that the protein of SEQ ED NO: 179 may play a role in the lipid metabolism
and/or in male fertility. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, hyperlipidemia, hypercholesterolemia, atherosclerosis, cardiovascular disorders such as coronary heart disease, and neurodegenerative disorders such as Alzheimer's disease or dementia, and disorders linked to male fertility.

25 Protein of SEQ ID NO: 227

The protein of SEQ ID NO: 227 encoded by the extended cDNA SEQ ID NO: 126 exhibits extensive homology to the ATP binding region of a whole family of serine/threonine protein kinases belonging to the CDC2/CDC28 subfamily. The PROSITE signature characteristic for this domain is present in the protein of the invention from positions 10 to 34.

Taken together, these data suggest that the protein of SEQ ED NO: 158 may bind ATP, and even be a protein 30 kinase. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, cardiovascular disorders, hypertension, renal injury and repair and septic shock.

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Although this invention has been described in terms of certain preferred embodiments, other embodiments which will be apparent to those of ordinary skill in the art in view of the disclosure herein are also within the scope of this invention. Accordingly, the scope of the invention is intended to be defined only by reference to the appended claims.

As discussed above, the extended cDNAs of the present invention or portions thereof can be used for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to 10 compare with endogenous ONA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related ONA sequences; as a source of information to derive PCR primers for genetic fingerprinting; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination for expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or 15 potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins or polypeptides provided by the present invention can similarly be used in assays to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit 20 another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning; A Laboratory Manual", 2d ed., Cole Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology; Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a

nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

SEQUENCE LISTING FREE TEXT

The following free text appears in the accompanying Sequence Listing:

In vitro transcription product

oligonucleotide

5 promoter

transcription start site

Von Heijne matrix

Score

matinspector prediction

10 name

TABLE

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41 U.S. Provisional Patent Application Serial No. 60/081,563, filed Agr. 13, 1998 72 42 U.S. Provisional Patent Application Serial No. 60/081,563, filed Agr. 13, 1998 52 43 U.S. Provisional Patent Application Serial No. 60/081,563, filed Dec. 17, 1997 78 44 U.S. Provisional Patent Application Serial No. 60/081,563, filed Dec. 17, 1997 78 45 U.S. Provisional Patent Application Serial No. 60/081,563, filed Dec. 17, 1997 79 46 U.S. Provisional Patent Application Serial No. 60/081,563, filed Dec. 17, 1997 67 47 U.S. Provisional Patent Application Serial No. 60/089,957, filed Dec. 17, 1997 82 48 U.S. Provisional Patent Application Serial No. 60/089,957, filed Dec. 17, 1997 82 49 U.S. Provisional Patent Application Serial No. 60/089,957, filed Dec. 17, 1997 82 50 U.S. Provisional Patent Application Serial No. 60/089,957, filed Dec. 17, 1998 51 51 U.S. Provisional Patent Application Serial No. 60/089,957, filed Dec. 17, 1997 195 52 U.S. Provisional Patent Application Serial No. 60/089,957, filed Dec. 17, 1997 195 53 U.S. Provisional Patent Application Serial No. 60/089,957, filed Dec. 17, 1997 46 68 U.S. Provisional Patent Application Serial No. 60/089,957, filed Dec. 17, 1997 68 69 U.S. Provisional Patent Application Serial No. 60/089,957, filed Dec. 17, 1997 68 60 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 48 61 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 55 62 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 56 63 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 57 64 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 50 65 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 50 66 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 50 67 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 51 68 U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998 53 69 U.S. Provi	SEQ ID NO. in Present application	Provisional Application Disclosing Sequence	SEQ ID NO. in provisional application
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361	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	194
362	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	195
363	L.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	196
364	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	197
365	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	1998
366	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	199
367	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	200
368	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	201
369	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	202
370	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	203
371	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	204
372	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	205
373	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	206
374	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	207
375	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	208
376	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	209
377	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	210

TABLE II: Parameters used for each step of EST analysis

	} :	Search Charac	teristics	Selection Characteristics	
Step	Program	Strand	Parameters	Identity (%))	Length (bp)
Miscellaneous	Blastn	both	S=61 X=16	90	17
tRNA	Fasta	both		80	60
rRNA	Blastn	both	S=108	80	40
mtRNA	Blastn	both	S-108	80	40
Procaryotic	Blastn	both	S-144	90	40
Fungal	Blastn	both	S=144	90	40
Alu	fasta*	both		70	40
L1	Blastn	both	S=72	70	40
Repeats	Blastn	both	S-72	70	40
Promoters	Blastn	top	S=54 X=16	90	15⊥
Vertebrate	fasta*	both	S=108	90	30
ESTs	Blatsn	both	S=108 X=16	90	30
Proteins	blastxŋ	top	E-0.001		

^{*} use "Quick Fast" Database Scanner

 $oldsymbol{\perp}$ alignment further constrained to begin closer than 10bp to EST\5' end

⁵ η using BLOSUM62 substitution matrix

TABLE III: Parameters used for each step of extended cDNA analysis

	Search characte	ristics		Selection	n characteristic	:s
Step	Program	Strand	Parameters	Identity (%)	Length (bp)	Comments
miscellaneous •	FASTA	both		90	15	
tRNA ^{\$}	FASTA	both		80	90	
rRNA*	BLASTN	both	S-108	80	40	
mtRNA*	BLASTN	both	S-108	80	40	
Procaryotic*	BLASTN	both	S-144	90	40	
Fungal*	BLASTN	both	S=144	90	40	
Alu*	BLASTN	both	S-72	70	40	max 5 matches, masking
L1*	BLASTN	both	S-72	70	40	max 5 matches, masking
Repeats*	BLASTN	both	S=72	70	40	masking
PolyA	BLAST2N	top	W-6,S-10,E-1000	90	8	in the last 20 nucleotides
Polyadenylati on signal		top	AATAAA allowing 1 mismatch			in the 50 nucleotides preceding the 5' end of the
Vertebrate*	BLASTN then FASTA	both		90 then 70	30	first BLASTN and then FASTA on matching sequences
ESTs*	BLAST2N	both	•	90	30	
Geneseq	BLASTN	bath	W-8, B-10	90	30	
ORF	BLASTP	top	W-8, B-10		•	on ORF proteins, max 10
Proteins.*	BLASTX	top	E=0.001	70	30	

steps common to EST analysis and using the same algorithms and parameters
 steps also used in EST analysis but with different algorithms and/or parameters

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TABLE IV

							
ld	FCS Location	SigPep Location	;	Stop	PolyA Signal	PolyA Site Location	n
			Polypeptide Location	Codon	Location		
40	7 through 471	7 through 99	100 through 471	Location 472	537 through 542	554 through 568	_
41	168 through 332		168 through 332	333	557 through 562	334 (1)(1)(1)(1)	_
42	51 through 251	51 through 110	111 through 251	252	849 through 854	882 through 895	
43	20 through 613	20 through 82	83 through 613	614			_
44	12 through 416	12 through 86	87 through 416	417	425 through 430	445 through 458	_
45	276 through 1040	276 through 485	486 through 1040	1041		2024 through 2036	_
46	443 through 619	443 through 589	590 through 619	620		1267 through 1276	_
47	206 through 747	· · · · · · · · · · · · · · · · · · ·	206 through 747	- .	 .		+
48	36 through 521	36 through 104	105 through 521	522	528 through 533	548 through 561	4
49	36 through 395	36 through 104	105 through 395	396	599 through 604	619 through 632	$\frac{1}{2}$
50	21 through 41		21 through 41	42	328 through 333	357 through 370	\dashv
51	35 through 631	35 through 160	161 through 631	632	901 through 906	979 through 994	┨
52	271 through 399		271 through 399	400			4
53	103 through 252	103 through 213	214 through 252	253		588 through 597	$\frac{1}{2}$
54	2 through 460	1.	2 through 460	461	713 through 718	735 through 748	$\frac{1}{1}$
55	31 through 231		31 through 231	232	769 through 774	690 through 703	$\frac{1}{1}$
56	305 through 565		305 through 565	566	694 through 699	713 through 725	$\left\{ \right.$
57	124 through 873	124 through 378	379 through 873	874	1673 through 1678	1694 through 1705	$\left\{ \right.$
58	135 through 206		135 through 206	207	850 through 855	1056 through 1069	$\left\{ \right.$
59	135 through 818	·	135 through 818	819	909 through 914	1071 through 1084	-
60	33 through 290	33 through 92	93 through 290	291			ļ
61	485 through 616		485 through 616	617		669 through 682	
62	54 through 995	54 through 227	228 through 995	996	1130 through 1135	1181 through 1191	
63	657 through 923	657 through 896	897 through 923	924	957 through 962	974 through 1008	
64	18 through 311	18 through 62	63 through 311	312			
65	151 through 426	151 through 258	259 through 426	427	505 through 510	527 through 538	
66	10 through 1062	10 through 57	58 through 1062	1063	1710 through 1715	1735 through 1747	
67	. 78 through 491	78 through 218	219 through 491	492	1652 through 1657	1673 through 1686	
68	69 through 371	69 through 287	288 through 371	372	510 through 515	530 through 542	
69	2 through 757	2 through 205	206 through 757	758		1160 through 1174	
70	2 through 1051	2 through 205	206 through 1051	1052	1248 through 1253	1272 through 1285	
71	2 through 1171	2 through 205	206 through 1171	1172	1368 through 1373	1386 through 1398	
72	42 through 611	42 through 287	288 through 611	612	787 through 792	808 through 821	١.
73	62 through 916	62 through 757	758 through 916			904 through 916	
74	62 through 520	-	62 through 520	521	1124 through 1129	1141 through 1153	
75	21 through 167		21 through 167	168			
76	22 through 318		94 through 318	319	497 through 502	516 through 526	
77	8 through 292	8 through 118	119 through 292	293	317 through 322	339 through 352	
78	16 through 378		85 through 378	379	502 through 507	522 through 542	
		, <u></u>					

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CONT. TABLE IV

Cur	NT. TABLE IV					•
79	57 through 233	•	57 through 233	· · ·	·	
80	83 through 340	83 through 124	125 through 340	341	573 through 578	607 through 660
81	47 through 541	47 through 220	221 through 541	542	•	597 through 605
82	46 through 285	46 through 150	151 through 285	286	364 through 369	385 through 396
83	22 through 240	22 through 84	85 through 240	241	397 through 402	421 through 432
84	89 through 382		89 through 382	383	•	408 through 420
85	80 through 415	80 through 142	143 through 415	416	471 through 476	488 through 501
86	152 through 361	152 through 283	284 through 361	362	•	· ·
87	32 through 307	32 through 70	71 through 307	308	1240 through 1245	1261 through 1272
88	114 through 734	114 through 239	240 through 734	735	768 through 773	793 through 804
89	199 through 802		199 through 802		780 through 785	791 through 802
90	38 through 1174	38 through 148	149 through 1174	1175	1452 through 1457	1478 through 1490
91	26 through 361	•	26 through 361	1.		350 through 361
92	3 through 131	•	3 through 131	132	·	591 through 605
93	33 through 185	33 through 80	81 through 185	186	570 through 575	586 through 591
94	184 through 915	184 through 237	238 through 915	916	1119 through 1124	1139 through 1150
95	58 through 1116	58 through 159	160 through 1116	1117	1486 through 1491	1504 through 1513
96	327 through 417	·	327 through 417	1.		404 through 417
97	63 through 398	63 through 206	207 through 398	399		
98	2 through 163		2 through 163	164	488 through 493	511 through 522
99	13 through 465	13 through 75	76 through 465	466	·	
100	20 through 703	20 through 94	95 through 703	704	1000 through 1005	1023 through 1041
101	103 through 294	103 through 243	244 through 294	295		
102	81 through 518	81 through 173	174 through 518	519		
103	66 through 326	·	66 through 326	327	1066 through 1071	1087 through 1098
104	170 through 289	170 through 250	251 through 289	290		
105	36 through 497		36 through 497	498	650 through 655	663 through 685
106	18 through 320		18 through 320	321	539 through 544	542 through 554
107	71 through 1438	71 through 136	137 through 1438	1439	1644 through 1649	1665 through 1678
108	25 through 318	25 through 75	76 through 318	319	452 through 457	482 through 494
109	84 through 332	84 through 170	171 through 332	333	•	702 through 714
110	32 through 718	32 through 100	101 through 718	719	770 through 775	793 through 805
111	26 through 481	26 through 88	89 through 481	482	755 through 760	775 through 787
112	26 through 562	26 through 187	188 through 562	563	·	
113	4 through 810	4 through 279	280 through 810	811	858 through 863	881 through 893
114	55 through 459	55 through 120	121 through 459	460	1444 through 1449	1462 through 1475
115	48 through 248	48 through 161	162 through 248	249	283 through 288	308 through 321
116	25 through 399	25 through 186	187 through 399	400	•	
117	10 through 1137	10 through 72	73 through 1137	1138	1144 through 1149	1162 through 1173
118	72 through 704	72 through 161	162 through 704	705	772 through 777	
119	44 through 505	44 through 223	224 through 505	506		
120	25 through 393	25 through 150	151 through 393	394	734 through 739	757 through 770

CONT. TABLE IV

<u> </u>	VI. TABLE IV					
121	58 through 1095	58 through 114	115 through 1095	1096	T.	1202 through 1213
122	31 through 660	31 through 90	91 through 660	661	1288 through 1293	1307 through 1318
123	31 through 582	31 through 90	91 through 582	583	816 through 821	840 through 853
124	15 through 695	15 through 80	81 through 695	696	795 through 800	814 through 826
125	74 through 295	74 through 196	197 through 295	296	545 through 550	561 through 571
126	440 through 659		440 through 659	1.	601 through 606	
127	38 through 283	38 through 85	86 through 283	284	257 through 262	
128	121 through 477	121 through 288	289 through 477	 		
129	2 through 163	•	2 through 163	164	292 through 297	310 through 323
130	46 through 675	46 through 87	88 through 675	676	1364 through 1369	1383 through 1392
131	62 through 385		62 through 385	386	974 through 979	987 through 999
132	422 through 550	422 through 475	476 through 550	551		714 through 725
133	124 through 231		124 through 231	232	•	387 through 400
134	131 through 1053	131 through 169	170 through 1053	1.	1019 through 1024	1.
135	86 through 403	86 through 181	182 through 403	404	1097 through 1102	1117 through 1128
136	37 through 162	37 through 93	94 through 162	163	224 through 229 .	243 through 254
137	31 through 381	31 through 90	91 through 381	382	1.	875 through 886
138	46 through 579	46 through 156	157 through 579	580	-	
139	92 through 471	92 through 172	173 through 471		454 through 459	458 through 471
140	154 through 675	154 through 498	499 through 675	676	819 through 824	338 through 849
242	18 through 173	18 through 77	78 through 173	174	864 through 869	882 through 893
243	17 through 595	17 through 85	86 through 595	596	820 through 825	840 through 851
244	89 through 334	89 through 130	131 through 334	335	462 through 467	484 through 495
245	21 through 614	21 through 83	84 through 614	615	849 through 854	873 through 884
246	94 through 573	94 through 258	259 through 573	574	862 through 867	886 through 897
247	74 through 397	74 through 127	128 through 397	398	472 through 477	507 through 518
248	51 through 242	51 through 116	117 through 242	243	319 through 324	339 through 350
249	111 through 191	111 through 155	156 through 191	192	965 through 970	986 through 996
250	45 through 602	45 through 107	108 through 602	603	828 through 833	850 through 860
251	24 through 560	24 through 101	102 through 560	561	563 through 568	583 through 593
252	109 through 558	109 through 273	274 through 558	559		1104 through 1114
253	128 through 835	128 through 220	221 through 835	836	1145 through 1150	1170 through 1181
254	59 through 505	59 through 358	359 through 505	506	1042 through 1047	1062 through 1073
255	1 through 207	1 through 147	148 through 207	208	784 through 789	807 through 818
256	12 through 734	12 through 101	102 through 734	.735	914 through 919	961 through 971
257	378 through 518	378 through 467	468 through 518	519	607 through 612	628 through 640
258	110 through 304	110 through 193	194 through 304	305	708 through 713	732 through 743
259	201 through 419	201 through 272	273 through 419	420	601 through 606	627 through 637
260	123 through 302	123 through 176	177 through 302	303	1279 through 1284	1301 through 1312
261	98 through 673	98 through 376	377 through 673	674	•	1025 through 1035
262	17 through 463	17 through 232	233 through 463	464	657 through 662	684 through 696
263	263 through 481	263 through 322	323 through 481	482		858 through 868
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CONT. TABLE IV

	NT. TABLE IV					
264		42 through 101	102 through 299	300		762 through 775
265	198 through 431	198 through 260	261 through 431	432	·	1064 through 1074
266	279 through 473	279 through 362	363 through 473	474	944 through 949	970 through 981
267	12 through 644	12 through 92	93 through 644	645	1002 through 1007	1020 through 1031
268	91 through 459	91 through 330	331 through 459	460		1271 through 1281
269	70 through 327	70 through 147	148 through 327	328	1741 through 1746	1763 through 1774
270	12 through 497	12 through 104	105 through 497	498	935 through 940	955 through 967
271	90 through 383	90 through 200	201 through 383	384	609 through 614	632 through 643
272	332 through 541	332 through 376	377 through 541	542	739 through 744	761 through 773
273	43 through 222	43 through 177	178 through 222	223	530 through 535	555 through 566
274	115 through 231	115 through 180	181 through 231	232	419 through 424	445 through 455
275	232 through 384	232 through 300	301 through 384	385	650 through 655	662 through 673
276	143 through 427	143 through 286	287 through 427	428	606 through 611	628 through 639
277	284 through 463	284 through 379	380 through 463	464		762 through 772
278	162 through 671	162 through 398	399 through 671	672	805 through 810	830 through 840
279	63 through 632	63 through 308	309 through 632	633	808 through 813	829 through 840
280	21 through 362	21 through 200	201 through 362	363	821 through 826	838 through 849
281	21 through 503	21 through 344	345 through 503	504	1305 through 1310	1330 through 1341
282	1 through 201	1 through 63	64 through 201	202	637 through 642	660 through 671
283	39 through 1034	39 through 134	135 through 1034	1035	1566 through 1571	1587 through 1597
284	69 through 263	69 through 125	126 through 263	264	1173 through 1178	1196 through 1205
285	115 through 285	115 through 204	205 through 285	286	505 through 510	525 through 536
286	90 through 344	90 through 140	141 through 344	345	500 through 505	515 through 527
287	57 through 311	57 through 107	108 through 311	312	467 through 472	482 through 493
288	96 through 302	96 through 182	183 through 302	303		501 through 514
289	161 through 526	161 through 328	329 through 526	527		799 through 811
290	210 through 332	210 through 299	300 through 332	333	594 through 599	613 through 625
291	212 through 361	212 through 319	320 through 361	362	650 through 655	673 through 684
292	75 through 482	75 through 128	129 through 482	483	595 through 600	618 through 627
293	50 through 631	50 through 244	245 through 631	632	777 through 782	801 through 812
294	154 through 576	154 through 360	361 through 576	577	737 through 742	763 through 775
295	154 through 897	154 through 360	361 through 897	898	1017 through 1022	1044 through 1054
296	146 through 292	146 through 253	254 through 292	293	395 through 400	433 through 444
297	126 through 383	126 through 167	168 through 383 .	384	726 through 731	743 through 754
298	66 through 497	66 through 239	240 through 497	498	594 through 599	618 through 629
299	49 through 411	49 through 96	97 through 411	412	732 through 737	750 through 763
300	49 through 534	49 through 96	97 through 534	535	593 through 598	612 through 623
301	86 through 415	86 through 145	146 through 415	416	540 through 545	560 through 571
302	56 through 268	56 through 100	101 through 268	269	584 through 589	601 through 612
303	32 through 328	32 through 103	104 through 328	329	508 through 513	528 through 539
304	21 through 527	21 through 95	96 through 527	528	921 through 926	953 through 963
305	147 through 647	147 through 374	375 through 647	648		668 through 681
					<u> </u>	

CONT. TABLE IV

	NT. TABLE IV					
306	3 262 through 471	262 through 306	307 through 471	472	663 through 668	682 through 693
307	74 through 1216	74 through 172	173 through 1216	1217	1627 through 1632	1640 through 1652
308	48 through 164	48 through 89	90 through 164	165	482 through 487	505 through 517
309	185 through 334	185 through 295	296 through 334	335	355 through 360	392 through 405
310	195 through 347	195 through 272	273 through 347	348	1037 through 1042	1071 through 1082
311	90 through 815	90 through 179	180 through 815	816	883 through 888	905 through 916
312	52 through 513	52 through 231	232 through 513	514	553 through 558	572 through 583
313	172 through 438	172 through 354	355 through 438	439	682 through 687	685 through 697
314	148 through 366	148 through 225	226 through 366	367	770 through 775	792 through 803
315	175 through 336	175 through 276	277 through 336	337	-	812 through 823
316	191 through 553	191 through 304	305 through 553	554	766 through 771	804 through 817
317	106 through 603	106 through 216	217 through 603	604		1102 through 1112
318	47 through 586	47 through 124	125 through 586	587	1583 through 1588	1614 through 1623
319	99 through 371	99 through 290	291 through 371	372	491 through 496	513 through 524
320	44 through 814	44 through 112	113 through 814	815		978 through 989
321	3 through 581	3 through 182	183 through 581	582		1006 through 1016
322	107 through 427	107 through 190	191 through 427	428	499 through 504	516 through 529
323	45 through 407	45 through 83	84 through 407	408	1008 through 1013	1032 through 1042
324	201 through 332	201 through 251	252 through 332	333		869 through 880
325	217 through 543	217 through 255	256 through 543.	544	-	1206 through 1217
326	18 through 446	18 through 140	141 through 446	447	930 through 935	948 through 959
327	29 through 724	29 through 118	119 through 724	725	886 through 891	910 through 920
328	404 through 586	404 through 466	467 through 586	587	1304 through 1309	1334 through 1344
329	331 through 432	331 through 387	388 through 432	433	548 through 553	573 through 585
330	59 through 703	59 through 220	221 through 703	704	886 through 891	903 through 914
331	672 through 752	672 through 722	723 through 752	753	1.	1150 through 1161
332	57 through 311	57 through 128	129 through 311	312	332 through 337	351 through 363
333	80 through 232	80 through 127	128 through 232	233	617 through 622	634 through 645
334	91 through 291	91 through 219	220 through 291	292	367 through 372	389 through 400
335	196 through 384	196 through 240	241 through 384	385	461 through 466	485 through 496
336	54 through 590	54 through 227	228 through 590	591	-	955 through 965
337	133 through 846	133 through 345	346 through 846	847		890 through 901
338	138 through 671	138 through 248	249 through 671	672	1319 through 1324	1338 through 1347
339	124 through 411	124 through 186	187 through 411	412	948 through 953	971 through 983
340	372 through 494	372 through 443	444 through 494	495	708 through 713	732 through 745
341	112 through 450	112 through 192	193 through 450	451	1053 through 1058	1095 through 1106
342	117 through 866	117 through 170	171 through 866	867	1159 through 1164	1178 through 1190
343	13 through 465	13 through 75	76 through 465	466	1035 through 1040	1060 through 1070
344	2 through 718	2 through 76	77 through 718	719	1170 through 1175	1203 through 1213
345	86 through 709	86 through 361	362 through 709	710	943 through 948	963 through 973
346	63 through 320	63 through 179	180 through 320	321	771 through 776	799 through 810
347	299 through 418	299 through 379	380 through 418	419	739 through 744	762 through 771
					308 44	· ve unough //1

CONT. TABLE IV

	NI. TABLE IV					
348		186 through 233	234 through 380	381	383 through 388	396 through 409
349		69 through 233	234 through 458	459	564 through 569	602 through 613
350	12 through 638	12 through 263	264 through 638	639	951 through 956	975 through 985
351	282 through 389	282 through 332	333 through 389	390	1413 through 1418	1437 through 1447
352	208 through 339	208 through 294	295 through 339	340		1631 through 1641
353	69 through 557	69 through 224	225 through 557	558	849 through 854	870 through 883
354	134 through 325	134 through 274	275 through 325	326		718 through 729
355	78 through 731	78 through 227	228 through 731	732	· ·	1002 through 1013
356	46 through 693	46 through 90	91 through 693	694	937 through 942	962 through 973
357	126 through 527	126 through 182	183 through 527	528	834 through 839	856 through 867
358	66 through 320	66 through 113	114 through 320	321	490 through 495	508 through 519
359	73 through 948	73 through 159	160 through 948	949		1016 through 1028
360	69 through 434	69 through 236	237 through 434	435	419 through 424	441 through 452
361	628 through 804	628 through 711	712 through 804	805		864 through 875
362	70 through 366	70 through 108	109 through 366	367	496 through 501	521 through 531
363	70 through 366	70 through 108	109 through 366	367		1233 through 1244
364	111 through 434	111 through 185	186 through 434	435		618 through 631
365	19 through 567	19 through 63	64 through 567	568	749 through 754	771 through 781
366	19 through 312	19 through 63	64 through 312	313	896 through 901	921 through 931
367	64 through 612	64 through 234	235 through 612	613		839 through 849
368	39 through 458	39 through 80	81 through 458	459	613 through 618	
369	9 through 185	9 through 50	51 through 185	186		633 through 644
370	14 through 316	14 through 121	122 through 316	317	442 through 447	906 through 918
371	70 through 1092	70 through 234 .	235 through 1092	1093	1475 through 1480	458 through 471
372	274 through 597	274 through 399	400 through 597	598	731 through 736	1493 through 1504
373	230 through 469	230 through 307	308 through 469	470	<u> </u>	754 through 765
374	72 through 545	72 through 203	204 through 545	546	1004 through 1009	1027 through 1040
375	36 through 425	36 through 119	120 through 425	426		1151 through 1162
376	155 through 751	155 through 340	341 through 751	752	1215 through 1220	1240 through 1250
377	46 through 585	46 through 120	121 through 585		912 through 917	937 through 947
l		10 through 120	141 01100111 365	586	584 through 589	606 through 619

TABLE V

TABLE V						
!d	Full Length Polypeptide Location	Signal Peptide Location	Mature Polypeptide Locati			
141	-31 through 124	-31 through -1	1 through 124			
142	1 through 55		1 through 55			
143	-20 through 47	-20 through -1	1 through 47			
144	-21 through 177	-21 through -1	1 through 177			
145	-25 through 110	-25 through -1	1 through 110			
146	-70 through 185	-70 through -1	1 through 185			
147	-49 through 10	-49 through -1	1 through 10			
148	1 through 180		1 through 180			
149	-23 through 139	-23 through -1	1 through 139			
150	-23 through 97	-23 through -1				
151	1 through 7		1 through 97 1 through 7			
152	-42 through 157	-42 through -1				
153	1 through 43		1 through 157			
154	-37 through 13	-37 through -1	1 through 43			
155	1 through 153	- Or through - I	1 through 13			
156	1 through 67	·	1 through 153			
157	1 through 87		1 through 67			
158	-85 through 165	95 through 1	1 through 87			
159	1 through 24	-85 through -1	1 through 165			
160	1 through 228		1 through 24			
161	-20 through 66	20 through 1	1 through 228			
162	1 through 44	-20 through -1	1 through 66			
163	-58 through 256		1 through 44			
164	-80 through 9	-58 through -1	1 through 256			
165	-15 through 83	-80 through -1	1 through 9			
166	-36 through 56	-15 through -1	1 through 83			
167	-16 through 335	-36 through -1	1 through 56			
168	-47 through 91	-16 through -1	1 through 335			
169	-73 through 28	-47 through -1	1 through 91			
170	-68 through 184	-73 through -1	1 through 28			
171	-68 through 282	-68 through -1	1 through 184			
172	-68 through 322	-68 through -1	1 through 282			
173	-82 through 108	-68 through -1	1 through 322			
174	-232 through 53	-82 through -1	1 through 108			
175		232 through -1	1 through 53			
176	1 through 153	·	1 through 153			
177	1 through 49 -24 through 75		1 through 49			
178	-37 through 58	-24 through -1	1 through 75			
179		-37 through -1	1 through 58			
80	-23 through 98 1 through 59	-23 through -1	1 through 98			
81			1 through 59			
82	-14 through 72	-14 through -1	1 through 72			
83	-58 through 107 -35 through 45	-58 through -1	1 through 107			
84		-35 through -1	1 through 45			
85	-21 through 52	-21 through -1	1 through 52			
86	1 through 98	· · · · · · · · · · · · · · · · · · ·	1 through 98			
87	-21 through 91	-21 through -1	1 through 91			
	-44 through 26	-44 through -1	1 through 26			
88	-13 through 79	-13 through -1	1 through 79			
89	-42 through 165	-42 through -1	1 through 165			
90	1 through 201	·	1 through 201			

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CONT. TABLE V

ONT. TABLE	<u>V</u>		•
191	-37 through 342	-37 through -1	1 through 342
192	1 through 112	•	1 through 112
193	1 through 43		1 through 43
194	-16 through 35	-16 through -1	1 through 35
195	-18 through 226	-18 through -1	1 through 226
196	-34 through 319	-34 through -1	1 through 319
197	1 through 30		1 through 30
198	-48 through 64	-48 through -1	1 through 64
199	1 through 54		1 through 54
200	-21 through 130	-21 through -1	1 through 130
201	-25 through 203	-25 through -1	
202	-47 through 17	-47 through -1	1 through 203
203	-31 through 115	-31 through -1	1 through 17
204	1 through 87	·	1 through 115
205	-27 through 13	-27 through -1	1 through 87
206	1 through 154	Z7 tirodgr - 1	1 through 13
207	1 through 101		1 through 154
208	-22 through 434	-22 through -1	1 through 101
209	-17 through 81	-17 through -1	1 through 434
210	-29 through 54		1 through 81
211	-23 through 206	-29 through -1	1 through 54
212	-21 through 131	-23 through -1	1 through 206
213	-54 through 125	-21 through -1	1 through 131
214	-92 through 177	-54 through -1	1 through 125
215	-22 through 113	-92 through -1	1 through 177
216	-38 through 29	-22 through -1	1 through 113
217	-54 through 71	-38 through -1"	1 through 29
218	-21 through 355	-54 through -1	1 through 71
219	-30 through 181	-21 through -1	1 through 355
220	-60 through 94	-30 through -1	1 through 181
221	-42 through 81	-60 through -1	1 through 94
222	-19 through 327	-42 through -1	1 through 81
223	-20 through 190	•19 through •1	1 through 327
224	-20 through 164	-20 through -1	1 through 190
225	-22 through 205	-20 through -1	1 through 164
226	-41 through 33	-22 through -1	1 through 205
227	1 through 73	-41 through -1	1 through 33
228	-16 through 66	1011	1 through 73
229	-56 through 63	-16 through -1	1 through 66
230	1 through 54	-56 through -1	1 through 63
231		<u> </u>	1 through 54
232	-14 through 196	-14 through -1	1 through 196
233	1 through 108	•	1 through 108
234	-18 through 25	-18 through -1	1 through 25
235	1 through 36	•	1 through 36
236	-13 through 294	-13 through -1	1 through 294
237	-32 through 74	-32 through -1	1 through 74
238	-19 through 23	-19 through -1	1 through 23
239	-20 through 97	-20 through -1	1 through 97
	-37 through 141	-37 through -1	1 through 141
240	-27 through 99	-27 through -1	1 through 99
241	-115 through 59	-115 through -1	1 through 59
378	-20 through 32	-20 through -1	1 through 32
379	-23 through 170	-23 through -1	1 through 170
380	-14 through 68	-14 through -1	1 through 68

CONT. TABLE V

CONT. TABLE V			
381	-21 through 177	-21 through -1	1 through 177
382	-55 through 105	-55 through -1	1 through 105
383	-18 through 90	-18 through -1	1 through 90
384	-22 through 42	-22 through -1	1 through 42
385	-15 through 12	-15 through -1	1 through 12
386	-21 through 165	-21 through -1	1 through 165
387	-26 through 153	-26 through -1	1 through 153
388	-55 through 95	-55 through -1	1 through 95
389	·31 through 205	-31 through -1	1 through 205
390	-100 through 49	-100 through -1	1 through 49
391	-49 through 20	-49 through -1	1 through 20
392	-30 through 211	-30 through -1	1 through 211
393	-30 through 17	-30 through -1	1 through 17
394	-28 through 37	-28 through -1	1 through 37
395	-24 through 49	-24 through -1	1 through 49
396	-18 through 42	-18 through -1	1 through 42
397	-93 through 99	-93 through -1	1 through 99
398	-72 through 77	-72 through -1	1 through 77
399	-20 through 53	-20 through -1	1 through 53
400	-20 through 66	-20 through -1	
401	-21 through 57	-21 through -1	1 through 66
402	-28 through 37	-28 through -1	1 through 57
403	-27 through 184	-27 through -1	1 through 37
404	-80 through 43		1 through 184
405	26 through 60	-80 through -1	1 through 43
406	-31 through 131	-26 through -1	1 through 60
407	-37 through 61	-31 through -1	1 through 131
408	15 through 55	-37 through -1	1 through 61
409	-45 through 15	-15 through -1 -45 through -1	1 through 55
410	-22 through 17		1 through 15
411	-23 through 28	-22 through -1	1 through 17
412	······	-23 through -1	1 through 28
413	-48 through 47	-48 through -1	1 through 47
414	-32 through 28	-32 through -1	1 through 28
415	-79 through 91	-79 through -1	1 through 91
416	-82 through 108	-82 through -1	1 through 108
417	-60 through 54	-60 through -1	1 through 54
417	-108 through 53	-108 through -1	1 through 53
	-21 through 46	-21 through -1	1 through 46
419	-32 through 300	-32 through -1	1 through 300
422	-19 through 46	-19 through -1	1 through 46
423	-30 through 27	-30 through -1	1 through 27
423	-17 through 68	-17 through -1	1 through 68
	-17 through 68	-17 through -1	1 through 68
425	29 through 40	-29 through -1	1 through 40
426	-56 through 66	-56 through -1	1 through 66
427	-30 through 11	-30 through -1	1 through 11
428	-36 through 14	-36 through -1	1 through 14
429	-18 through 118	-18 through -1	1 through 118
430	-65 through 129	-65 through -1	1 through 129
431	69 through 72	-69 through -1	1 through 72
432	69 through 179	-69 through -1	1 through 179
433	-36 through 13	-36 through -1	1 through 13
434	-14 through 72	-14 through -1	1 through 72
435	-58 through 86	-58 through -1	1 through 86

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CONT.	IAD	LC V

IT. TABLE V			
436	-16 through 105	-16 through -1	1 through 105
437	-16 through 146	-16 through -1	1 through 146
438	-20 through 90	-20 through -1	1 through 90
439	-15 through 56	-15 through -1	1 through 56
440	-24 through 75	-24 through -1	1 through 75
441	-25 through 144	-25 through -1	1 through 144
442	-76 through 91	·76 through ·1	1 through 91
443	-15 through 55	-15 through -1	1 through 55
444	-33 through 348	-33 through -1	1 through 348
445	-14 through 25	-14 through -1	1 through 25
446	-37 through 13	-37 through -1	1 through 13
447	-26 through 25	-26 through -1	1 through 25
448	-30 through 212	-30 through -1	1 through 212
449	-60 through 94	-60 through -1	
450	-61 through 28	-61 through -1	1 through 94
451	-26 through 47	-26 through -1	1 through 28
452	-34 through 20	-34 through -1	1 through 47
453	-38 through 83	-38 through -1	1 through 20
454	-37 through 129		1 through 83
455	-26 through 154	-37 through -1 -26 through -1	1 through 129
456	-64 through 27		1 through 154
457	-23 through 234	-64 through -1	1 through 27
458	-60 through 133	-23 through -1	1 through 234
459	-28 through 79	-60 through -1	1 through 133
460	-13 through 108	-28 through -1	1 through 79
461		·13 through ·1	1 through 108
462	-17 through 27	-17 through -1	1 through 27
463	-13 through 96	-13 through -1	1 through 96
464	-41 through 102	41 through 1	1 through 102
465	-30 through 202	-30 through -1	1 through 202
466	-21 through 40	-21 through -1	1 through 40
467	-19 through 15	-19 through -1	1 through 15
	-54 through 161	-54 through -1	1 through 161
468	-17 through 10	-17 through -1	1 through 10
469	-24 through 61	-24 through -1	1 through 61
470	-16 through 35	-16 through -1	1 through 35
471	-43 through 24	-43 through -1	1 through 24
472	-15 through 48	-15 through -1	1 through 48
473	-58 through 121	-58 through -1	1 through 121
474	-71 through 167	-71 through -1	1 through 167
475	-37 through 141	-37 through -1	1 through 141
476	-21 through 75	-21 through -1	1 through 75
477	-24 through 17	-24 through -1	1 through 17
478	-27 through 86	-27 through -1	1 through 86
179	-18 through 232	-18 through -1	1 through 232
180	-21 through 130	-21 through -1	1 through 130
181	-25 through 214	-25 through -1	1 through 214
182	-92 through 116	-92 through -1	1 through 116
183	-39 through 47	-39 through -1	1 through 47
184	-27 through 13	-27 through -1	1 through 13
85	-16 through 49	-16 through -1	1 through 49
86	-55 through 75	-55 through -1	1 through 75
87	-84 through 125	-84 through -1	
88	-17 through 19	-17 through -1	1 through 125 1 through 19
	-29 through 15	i conought.i	r cordona 19

490	-52 through 111	-52 through -1	
491	-47 through 17	-47 through -1	1 through 111
492	-50 through 168	-50 through -1	1 through 17
493	-15 through 201		1 through 168
494	-19 through 115	-15 through -1	1 through 201
495	-16 through 69	-19 through -1	1 through 115
496		-16 through -1	1 through 69
497	-29 through 263	-29 through -1	1 through 263
498	-56 through 66	-56 through -1	1 through 66
499	-28 through 31	-28 through -1	1 through 31
	-13 through 86	-13 through -1	1 through 86
500	-13 through 86	-13 through -1	1 through 86
501	-25 through 83	-25 through -1	1 through 83
502	-15 through 168	-15 through -1	1 through 168
503	-15 through 83	-15 through -1	1 through 83
504	-57 through 126	-57 through -1	1 through 126
505	-14 through 126	-14 through -1	
506	-14 through 45	-14 through -1	1 through 126
507	-36 through 65	-36 through -1	1 through 45
508	-55 through 286	-55 through -1	1 through 65
509	-42 through 66	-42 through -1	1 through 286
510	-26 through 54		1 through 66
511	-44 through 114	-26 through -1	1 through 54
512	-28 through 102	-44 through -1	1 through 114
513	-62 through 137	-28 through -1	1 through 102
514	-25 through 155	-62 through -1	1 through 137
<u> </u>	-25 mough 155	-25 through -1	1 through 155

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TABLE VI

		I MOLE VI
ld	Collection refs	Oeposit Name
40	ATCC # 98921	SignalTag 121-144
41	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
42	ATCC # 98921	SignalTag 121-144
43	ATCC # 98920	SignalTag 67-90
44	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
45	ATCC # 98920	SignalTag 67-90
46	ATCC # 98923	SignalTag 44-66
47	ATCC # 98920	SignalTag 67-90
48	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
49	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
50	ATCC # 98921	SignalTag 121-144
51	ATCC # 98921	SignalTag 121-144
52	ATCC # 98920	SignalTag 67-90
53	ATCC # 98923	SignalTag 44-66
54	ATCC # 98920	SignalTag 67-90
55	ATCC # 98920	SignalTag 67-90
6	ATCC # 98920	SignalTag 67-90
7	ATCC # 98921	SignalTag 121-144
8	ATCC # 98920	SignalTag 67-90
9	ATCC # 98920	SignalTag 67-90
0	ATCC # 98920	SignalTag 67-90
1	ATCC # 98923	SignalTag 44-66
2	ATCC # 98923	SignalTag 44-66
3	ATCC # 98923	SignalTag 44-66
4	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
5	ATCC # 98923	SignalTag 44-66
3	ATCC # 98921	SignalTag 121-144
7	ATCC # 98920	SignalTag 67-90
3	ATCC # 98920	SignalTag 67-90
)	ATCC # 98921	SignalTag 121-144
)	ATCC # 98921	SignalTag 121·144
	ATCC # 98921	SignalTag 121-144
!	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
	ATCC # 98923	SignalTag 44-66

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74	ATCC # 98923	SignalTag 44-66	
75	ATCC # 98920	SignalTag 67-90	
76	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
77	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
78	ATCC # 98921	SignalTag 121-144	
79	ATCC # 98923	SignalTag 44-66	
80	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
81	ATCC # 98921	SignalTag 121-144	
82	ATCC # 98920	SignalTag 67-90	
83	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	· <u></u>
84	ATCC # 98923	SignalTag 44-66	
85	ATCC # 98923	SignalTag 44-66	
86	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
87	ATCC # 98923	SignalTag 44-66	
88	ATCC # 98923	SignalTag 44-66	
89	ATCC # 98923	SignalTag 44-66	
90	ATCC # 98923	SignalTag 44-66	
91	ATCC # 98923	SignalTag 44-66	
92	ATCC # 98920	SignalTag 67-90	\neg
93	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
94	ATCC # 98923	SignalTag 44-66	
95	ATCC # 98923	SignalTag 44-66	
96	ATCC # 98920	SignalTag 67-90	
97	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
98	ATCC # 98921	SignalTag 121-144	\neg
99	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
100	ATCC # 98921	SignalTag 121-144	
101 ·	ATCC # 98920	SignalTag 67-90	
102	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
103	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
104	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
05	ATCC # 98921	SignalTag 121-144	
06	ATCC # 98920	SignalTag 67-90	
07	ATCC # 98920	SignalTag 67-90	\dashv
80	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	\neg
09	ATCC # 98923	SignalTag 44-66	-
10	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	\dashv

		SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
112	ATCC # 98920	SignalTag 67-90
113	ATCC # 98920	SignalTag 67-90
114	ATCC # 98923	SignalTag 44-66
115	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
116	ATCC # 98920	SignalTag 67-90
117	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
118	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
119	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
120	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
121	ATCC # 98923	SignalTag 44-66
122	ATCC # 98920	SignalTag 67-90
123	ATCC # 98920	
124	ATCC # 98922	SignalTag 67-90
125	ECACC # 98121506	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
		SignalTag 11121998
126	ECACC # 98121506	SignalTag 11121998
127	ECACC # 98121506	SignalTag 11121998
128	ECACC # 98121506	SignalTag 11121998
129	ECACC # 98121506	SignalTag 11121998
130	ECACC # 98121506	SignalTag 11121998
131	ECACC # 98121506	SignalTag 11121998
132	ECACC # 98121506	SignalTag 11121998
133	ECACC # 98121506	SignalTag 11121998
134	ECACC # 98121506	SignalTag 11121998
135	ECACC # 98121506	SignalTag 11121998
136	ECACC # 98121506	SignalTag 11121998
137	ECACC # 98121506	SignalTag 11121998
138	ECACC # 98121506	SignalTag 11121998
139	ECACC # 98121506	SignalTag 11121998
140	ECACC # 98121506	SignalTag 11121998

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TABLE VII

Internal designation number	SEQ ID NO	Type of sequence
20-5-2-C3-CL0_4	40	DNA
20-8-4-A11-CL2_6	41	DNA
21-1-4-F2-CL11_1	42	DNA
22-11-2-H9-CL1_1	43	DNA
25-7-3-D4-CL0_2	44	DNA
26-27-3-D7-CLO_1	45	DNA
26-35-4-H9-CL1_1	46	DNA
26-45-2-C4-CL2_6	47	DNA
27-1-2-B3-CL0_1	48	DNA
27-1-2-B3-CL0_2	49	DNA
27-19-3-G7-CL11_2	50	DNA
33-10-4-E2-CL13_4	51	DNA
33-10-4-H2-CL2_2	52	DNA
33-110-4-A5-CL1_1	53	DNA
33-13-1-C1-CL1_1	54	DNA
33-30-2-A6-CL0_1	55	DNA
33-35-4-F4-CL1_2	56	DNA
33-35-4-G1-CL1_2	57	DNA
33-36-3-E2-CL1_1	58	DNA
33-36-3-E2-CL1_2	59	DNA
33-36-3-F2-CL2_2	60	DNA
33-4-2-G5-CL2_1	61	DNA
33-49-1-H4-CL1_1	62	DNA
33-66-2-B10-CL4_1	63	DNA
33-97-4-G8-CL2_2	64	DNA
33-98-4-C1-CL1_3	-65	DNA
47-14-1-C3-CLO_5	66	DNA
47-15-1-E11-CLO_1	67	DNA
47-15-1-H8-CL0_2	68	DNA
48-1-1-H7-CLO_1	69	DNA
48-1-1-H7-CLO_4	70	DNA
48-1-1-H7-CLO_5	71	DNA
48-3-1-H9-CLO_6	72	DNA
48-54-1-G9-CL2_1	73	DNA

48-54-1-G9-CL3_1	74	DNA
48-7-4-H2-CL2_2	75	DNA
51-11-3-D5-CL1_3	76	DNA
51-11-3-G9-CLO_1	77	DNA
51-15-4-A12-CL11_3	78	DNA
51-17-4-A4-CL3_1	79	DNA
51-2-3-F10-CL1_5	80	DNA
51-2-4-F5-CL11_2	81	DNA
51-27-4-F2-CL0_2	82	DNA
51-34-3-F8-CLO_2	83	DNA
57-1-4-E2-CL1_2	84	DNA
57-19-2-G8-CL2_1	85	DNA
57-27-3-G10-CL2_2	86	DNA
58-33-3-B4-CL1_2	87	DNA
58-34-3-C9-CL1_2	88	DNA
58-4-4-G2-CL2_1	89	DNA
58-48-1-G3-CL2_4	90	DNA
58-6-1-H4-CL1_1	91	DNA
60-12-1-E11-CL1_2	92	DNA
65-4-4-H3-CL1_1	93	DNA
74-5-1-E4-CL1_2	94	DNA
76-13-3-A9-CL1_2	95	DNA
76-16-1-D6-CL1_1	96	DNA
76-28-3-A12-CL1_5	97	DNA
76-42-2-F3-CL0_1	98	DNA
77·16-4·G3·CL1_3	99	DNA
77-39-4-H4-CL11_4	100	DNA
78-24-3-H4-CL2_1	101	DNA
78-27-3-D1-CL1_6	102	DNA
78-28-3-D2-CL0_2	103	DNA
78-7-1-G5-CL2_6	104	DNA
84-3-1-G10-CL11_6	105	DNA
58-48-4-E2-CLO_1	106	DNA
23-12-2-G6-CL1_2	107	DNA
25-8-4-B12-CLO_5	108	DNA
26-44-3-C5-CL2_1	109	DNA
27-1-2-B3-CL0 3	110	DNA

		-125-
30-12-3-G5-CL0_1	111	DNA
33·106-2·F10·CL1_3	112	DNA
33-28-4-D1-CLO_1	. 113	DNA
33-31-3-C8-CL2_1	114	DNA
48-24-1-D2-CL3_2	115	DNA
48-46-4-A11-CL1_4	116	DNA
51-1-4-C1-CL0_2	117	DNA
51-39-3-H2-CL1_2	118	DNA
51-42-3-F9-CL1_1	119	DNA
51-5-3-G2-CLO_4	120	DNA
57-18-4-H5-CL2_1	121	DNA
76-23-3-G8-CL1_1	122	DNA
76-23-3-G8-CL1_3	123	DNA
78-8-3-E6-CLO_1	124	DNA
19-10-1-C2-CL1_3	125	DNA
33-11-1-B11-CL1_2	126	DNA
33-113-2-B8-CL1_2	127	DNA
33-19-1-C11-CL1_1	128	DNA
33-61-2-F6-CLO_2	129	DNA
47-4-4-C6-CL2_2	130	DNA
48-54-1-G9-CL1_1	131	DNA
51-43-3-G3-CLO_1	132	DNA
55-1-3-D11-CLO_1	133	DNA
58-14-2-D3-CL1_2	134	DNA
58-35-2-B6-CL2_3	135	DNA
76-18-1-F6-CL1_1	136	DNA
76-23-3-G8-CL2_2	137	DNA
76-30-3-B7-CL1_1	138	DNA
78-21-3-G7-CL2_1	139	DNA
58-45-4-B11-CL13_2	140	DNA
20-5-2-C3-CL0_4	141	PRT
20-8-4-A11-CL2_6	142	PRT
21-1-4-F2-CL11_1	143	PRT
22-11-2-H9-CL1_1	144	PRT
25-7-3-D4-CLO_2	145	PRT
26-27-3-D7-CLO_1	146	PRT
26-35-4-H9-CL1_1	147	PRT
		

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26-45-2-C4-CL2_6	148	PRT
27-1-2-B3-CLO_1	149	PRT
27-1-2-B3-CLO_2	150	PRT
27-19-3-G7-CL11_2	151	PRT
33-10-4-E2-CL13_4	152	PRT
33-10-4-H2-CL2_2	153	PRT
33-110-4-A5-CL1_1	154	PRT
33-13-1-C1-CL1_1	155	PRT
33-30-2-A6-CLO_1	156	PRT
33-35-4-F4-CL1_2	157	PRT
33-35-4-G1-CL1_2	158	PRT
33-36-3-E2-CL1_1	159	PRT
33-36-3-E2-CL1_2	160	PRT
33-36-3-F2-CL2_2	161	PRT
33-4-2-G5-CL2_1	162	PRT
33-49-1-H4-CL1_1	163	PRT
33-66-2-B10-CL4_1	164	PRT
33-97-4-G8-CL2_2	165	PRT
33-98-4-C1-CL1_3	166	PRT
47-14-1-C3-CLO_5	167	PRT
47-15-1-E11-CLO_1	168	PRT
47-15-1-H8-CLO_2	169	PRT
48-1-1-H7-CLO_1	170	PRT
48-1-1-H7-CLO_4	171	PRT
48-1-1-H7-CLO_5	172	PRT
48-3-1-H9-CLO_6	173	PRT
48-54-1-G9-CL2_1	174	PRT
48-54-1-G9-CL3_1	175	PRT
48-7-4-H2-CL2_2	176	PRT
51-11-3-D5-CL1_3	177	PRT
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51-15-4-A12-CL11_3	179	PRT
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51-2-3-F10-CL1_5	181	PRT
51-2-4-F5-CL11_2	182	PRT
51-27-4-F2-CL0_2	183	PRT
51-34-3-F8-CLO_2	184	PRT

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57-1-4-E2-CL1_2	185	PRT
57-19-2-G8-CL2_1	186	PRT
57-27-3-G10-CL2_2	187	PRT
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58-34-3-C9-CL1_2	189	PRT
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58-48-1-G3-CL2_4	191	PRT
58-6-1-H4-CL1_1	192	PRT
60-12-1-E11-CL1_2	193	PRT
65-4-4-H3-CL1_1	194	PRT
74-5-1-E4-CL1_2	195	PRT
76-13-3-A9-CL1_2	196	PRT
76-16-1-D6-CL1_1	197	PRT
76-28-3-A12-CL1_5	198	PRT
76-42-2-F3-CLO_1	199	PRT
77-16-4- G 3- C L1_3	200	PRT
77-39-4-H4-CL11_4	201	PRT
78-24-3-H4-CL2_1	202	PRT
78-27-3-D1-CL1_6	203	PRT
78-28-3-D2-CLO_2	204	PRT
78-7-1-G5-CL2_6	205	PRT
84-3-1-G10-CL11_6	206	PRT
58-48-4-E2-CLO_1	207	PRT
23-12-2-G6-CL1_2	208	PRT
25-8-4-B12-CLO_5	209	PRT
26-44-3-C5-CL2_1	210	PRT .
27-1-2-B3-CLO_3	211	PRT
30-12-3-G5-CL0_1	212	PRT
33-106-2-F10-CL1_3	213	PRT
33-28-4-D1-CLO_1	214	PRT .
33-31-3-C8-CL2_1	215	PRT
48-24-1-D2-CL3_2	216	PRT
48-46-4-A11-CL1_4	217	PRT
51-1-4-C1-CLO_2	218	PRT
51-39-3-H2-CL1_2	219	PRT
51-42-3-F9-CL1_1	220	PRT
51-5-3-G2-CLO_4	221	PRT

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57-18-4-H5-CL2_1	222	PRT
76-23-3-G8-CL1_1	223	PRT
76-23-3-G8-CL1_3	224 -	PRT
78-8-3-E6-CLO_1	225	PRT
19-10-1-C2-CL1_3	226	PRT
33-11-1-B11-CL1_2	227	PRT
33-113-2-B8-CL1_2	228	PRT
33-19-1-C11-CL1_1	229	PRT
33-61-2-F6-CLO_2	230	PRT
47-4-4-C6-CL2_2	231	PRT
48-54-1-G9-CL1_1	232	PRT
51-43-3-G3-CLO_1	233	PRT
55-1-3-D11-CLO_1	234	PRT
58-14-2-D3-CL1_2	235	PRT
58-35-2-B6-CL2_3	236	PRT
76-18-1-F6-CL1_1	237	PRT
76-23-3-G8-CL2_2	238	PRT
76-30-3-B7-CL1_1	239	PRT ·
78-21-3-G7-CL2_1	240	PRT
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20-8-4-A11-FL2	243	DNA
22-6-2-C1-FL2	244	DNA
22-11-2-H9-FL1	245	DNA
23-8-3-B1-FL1	246	DNA
24-3-3-C6-FL1	247	DNA
24-4-1-H3-FL1	248	DNA
26-45-2-C4-FL2	249	DNA
26-48-1-H10-FL1	250	DNA
26-49-1-A5-FL2	251	DNA
30-6-4-E3-FL3	252	DNA
33-6-1-G11-FL1	253	DNA
33-8-1-A3-FL2	254	DNA
33-11-3-C6-FL1	255	DNA
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33-21-2-D5-FL1	257	DNA
33-26-4-E10-FL1	258	DNA
		

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33-30-4-C4-FL1	262	DNA
33-35-4-F4-FL1	263	DNA
33-36-3-F2-FL2	264	DNA
33-52-4-F9-FL2	265	DNA
33-52-4-H3-FL1	266	DNA
33-59-1-B7-FL1	267	DNA
33-71-1-A8-FL1	268	DNA
33-72-2-B2-FL1	269	DNA
33-105-2-C3-FL1	270	DNA
33-107-4-C3-FL1	271	DNA
33-110-2-G4-FL1	272	DNA
47-7-4-D2-FL2	273	DNA
47-10-2-G12-FL1	274	DNA
47-14-3-D8-FL1	275	DNA
47-18-3-C2-FL1	276	DNA
47-18-3-G5-FL2	277	DNA
47-18-4-E3-FL2	278	DNA
48-3-1-H9-FL3	279	DNA
48-4-2-H3-FL1	280	DNA
48-6-1-C9-FL1	281	DNA
48-7-4-H2-FL2	282	DNA
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48-47-3-A5-FL1	292	DNA
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51-2-4-F5-FL1	298	DNA
51-3-3-B10-FL2	299	DNA
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51-7-3-G3-FL1	301	DNA
51-10-3-D11-FL1	302	DNA
51-11-3-D5-FL1	303	DNA
51-13-1-F7-FL3	304	DNA
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51-17-4-A4-FL1	306	DNA
51-18-1-C3-FL1	307	DNA
51-25-3-F3-FL1	308	DNA
51-27-1-E8-FL1	309	DNA
51-28-2-G1-FL2	310	DNA
51-39-3-H2-FL1	311	DNA
51-42-3-F9-FL1	312	DNA
51-44-4-H4-FL1	313	DNA
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58-11-2-G8-FL2	322	DNA
58-36-3-A9-FL2	323	DNA
58-38-1-A2-FL2	324	DNA
58-38-1-E5-FL1	325	DNA
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58-53-2-B12-FL2	328	DNA
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60-16-3-A6-FL1	330	DNA
60-17-3-G8-FL2	331	DNA
62-5-4-B10-FL1	332	DNA

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76-4-1-G5-FL1	335	DNA
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76-16-4-C9-FL3	337	DNA
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77-5-4-E7-FL1	340	DNA
77-11-1-A3-FL1	341	DNA
77-16-3-D7-FL1	342	DNA
77-16-4-G3-FL1	343	DNA
77-25-1-A6-FL1	344	DNA
77-26-2-F2-FL3	345	DNA
78-6-2-E3-FL2	346	DNA
78-7-1-G5-FL2	347	DNA
78-16-2-C2-FL1	348	DNA
78-18-3-B4-FL3	349	DNA
78-20-1-G11-FL1	350	DNA
78-22-3-E10-FL1	351	DNA
78-24-2-B8-FL1	352	DNA
78-24-3-A8-FL1	353	DNA
78-24-3-H4-FL2	354	DNA
78-25-1-F11-FL1	355	DNA
78-26-1-B5-FL1	356	DNA
78-27-3-D1-FL1	357	DNA
78-29-1-B2-FL1	358	DNA
78-29-4-B6-FL1	359	DNA
14-1-3-E6-FL1	360	DNA
30-9-1-G8-FL2	361	DNA
33-10-4-H2-FL2	362	DNA
33-10-4-H2-FL1	363	DNA
74-10-3-C9-FL2	364	DNA
33-97-4-G8-FL3	365	DNA
33-97-4-G8-FL2	366	DNA
33-104-4-H4-FL1	367	DNA
47-2-3-B3-FL1	368	DNA
47-37-4-G11-FL1	369	DNA

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47-7-4-D2-FL2	409	PRT	
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47-14-3-D8-FL1	411	PRT	
47-18-3-C2-FL1	412	PRT	
47-18-3-G5-FL2	413	PRT	
47-18-4-E3-FL2	414	PRT	
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48-6-1- C9-FL 1	417	PRT	
48-7-4-H2-FL2	418	PRT	
48-8-1-D8-FL3	419	PRT	
48-13-3-H8-FL1	420	PRT	
48-19-3-A7-FL1	421	PRT	
48-19-3-G1-FL1	422	PRT	
48-25-4-D8-FL1	423	PRT	
48-21-4-H4-FL1	424	PRT	
48-26-3-B8-FL2	425	PRT	
48-29-1-E2-FL1	426	PRT	
48-31-3-F7-FL1	427	PRT	
48-47-3-A5-FL1	428	PRT	
51-1-1-G12-FL1	429	PRT	
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51-1-4-E9-FL2	431	PRT	
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51-2-4-F5-FL1	434	PRT	
51-3-3-B10-FL2	435	PRT	
51-3-3-B10-FL3	436	PRT .	
51-7-3-G3-FL1	437	PRT	
51-10-3-D11-FL1	438	PRT	
51-11-3-D5-FL1	439	PRT	
51-13-1-F7-FL3	440	PRT	
51-15-4-H10-FL1	441	PRT	
51-17-4-A4-FL1	442	PRT	
51-18-1-C3-FL1	443	PRT	

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51-25-3-F3-FL1	444	PRT
51-27-1-E8-FL1	445	PRT
51-28-2-G1-FL2	446	PRT
51-39-3-H2-FL1	447	PRT
51-42-3-F9-FL1	448	PRT
51-44-4-H4-FL1	449	PRT
55-1-3-H10-FL1	450	PRT
55-5-4-A6-FL1	451	PRT
58-26-3-D1-FL1	452	PRT
57-18-1-D5-FL1	453	PRT
57-27-3-A11-FL1	454	PRT
57-27-3-G10-FL2	455	PRT
58-10-3-D12-FL1	456	PRT
58-11-1-G10-FL1	457	PRT
58-11-2-G8-FL2	458	PRT
58-36-3-A9-FL2	459	PRT
58-38-1-A2-FL2	460	PRT
58-38-1-E5-FL1	461	PRT
58-44-2-B3-FL3	462	PRT
58-45-3-H11-FL1	463	PRT
58-53-2-B12-FL2	464	PRT
59-9:4-A10-FL1	465	PRT
60-16-3-A6-FL1	466	PRT
60-17-3-G8-FL2	467	PRT
62-5-4-B10-FL1	468	PRT
65-4-4-H3-FL1	469	PRT
74-3-1-B9-FL1	470	PRT
76-4-1-G5-FL1	471	PRT
76-7-3-A12-FL1	472	PRT
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76-30-3-B7-FL1	474	PRT
77-5-1-C2-FL1	475	PRT
77-5-4-E7-FL1	476	PRT
77-11-1-A3-FL1	477	PRT
77-16-3-D7-FL1	478	PRT
77-16-4-G3-FL1	479	PRT
77-25-1-A6-FL1	480	PRT

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	481 482 483 484 485 486 487 488 489 490 491 492 493 494 495 496 497 498 499 500 501 502 503 504 505 506 507 508 509 510 511 512	

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TABLE VIII

ID	Locations	PROSITE Signature Name			
195	110-121	Aldehyde dehydrogenases csyteine active site			
221	28-37	ATP synthase alpha and beta subunits signature			
223	171-181	Regulator of chromosome condensation (RCC1) signature 2			
225	90-112	Phosphatidylethanolamine-binding protein family signature			
226	10-34	Protein kinases ATP-binding region signature			

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WHAT IS CLAIMED IS:

- 1. A purified or isolated nucleic acid comprising the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary thereto.
- 2. A purified or isolated nucleic acid comprising at least 10 consecutive bases of the sequence of one of SEQ ID NOs: 40-140 and 242-377 or one of the sequences complementary thereto.
 - 3. A purified or isolated nucleic acid comprising the full coding sequences of one of SEQ ID NOs: 40, 42-44, 46, 48, 49, 51, 53, 60, 62-72, 76-78, 80-83, 85-88, 90, 93, 94, 97, 99-102, 104, 107-125, 127, 132, 135-138, 140 and 242-377wherein the full coding sequence comprises the sequence encoding signal peptide and the sequence encoding mature protein.
- 4. A purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode a mature protein.
- 5. A purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40, 42-46, 48, 49, 51, 53, 57, 60, 62-73, 76-78, 80-83, 85-88, 90, 93-95, 97, 99-102, 104, 107-125, 127, 128, 130, 132, 134-140
 15 and 242-377 which encode the signal peptide.
 - 6. A purified or isolated nucleic acid encoding a polypeptide having the sequence of one of the sequences of SEO ID NOs: 141-241 and 378-513.
- A purified or isolated nucleic acid encoding a polypeptide having the sequence of a mature protein included in one of the sequences of SEO ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-20
 189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.
 - 8. A purified or isolated nucleic acid encoding a polypeptide having the sequence of a signal peptide included in one of the sequences of SEO ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.
 - A purified or isolated protein comprising the sequence of one of SEQ ID NOs: 141-241 and 378-513.
- A purified or isolated polypeptide comprising at least 10 consecutive amino acids of one of the sequences of SEO ID Nos: 141-241 and 378-513.
 - 11. An isolated or purified polypeptide comprising a signal peptide of one of the polypeptides of SEQ ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.
- 30 12. An isolated or purified polypeptide comprising a mature protein of one of the polypeptides of SEQ IO NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.
 - 13. A method of making a protein comprising one of the sequences of SEQ ID NO: 141-241 and 378-513, comprising the steps of:

cDNA.

obtaining a cDNA comprising one of the sequences of sequence of SEQ ID NO: 40-140 and 242-377; inserting said cDNA in an expression vector such that said cDNA is operably linked to a promoter; and introducing said expression vector into a host cell whereby said host cell produces the protein encoded by said

- 5 14. The method of Claim 13, further comprising the step of isolating said protein.
 - 15. A protein obtainable by the method of Claim 14.
 - 16. A host cell containing a recombinant nucleic acid of Claim 1.
 - 17. A purified or isolated antibody capable of specifically binding to a protein having the sequence of one of SEO ID NOs: 141-241 and 378-513.
- 10 18. In an array of polynucleotides of at least 15 nucleotides in length, the improvement comprising inclusion in said array of at least one of the sequences of SEQ ID NOs: 40-140 and 242-377, or one of the sequences complementary to the sequences of SEQ ID NOs: 40-140 and 242-377, or a fragment thereof of at least 15 consecutive nucleotides.
- 19. A purified or isolated nucleic acid of at least 15 bases capable of hybridizing under stringent conditions to the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary to one of the sequences of SEQ ID NDs: 40-140 and 242-377.
 - 20. A purified or isolated antibody capable of binding to a polypeptide comprising at least 10 consecutive amino acids of the sequence of one of SEO ID NDs: 141-241 and 378-513.

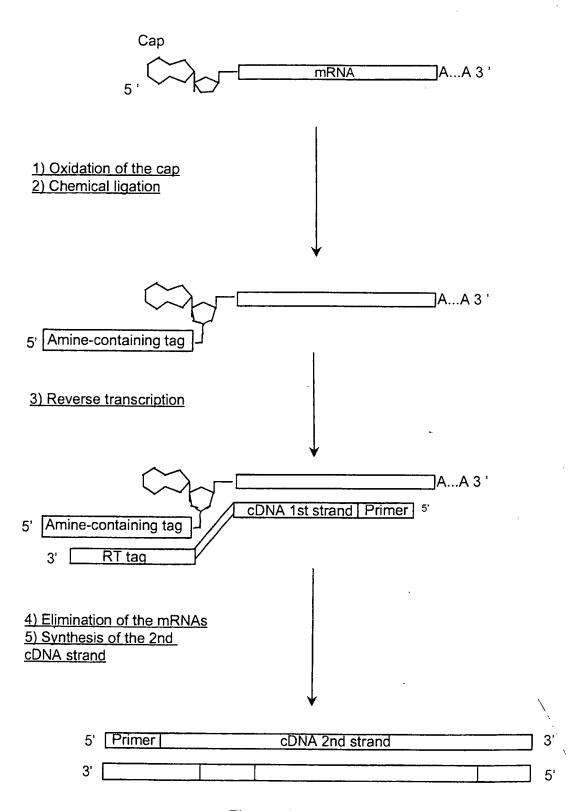
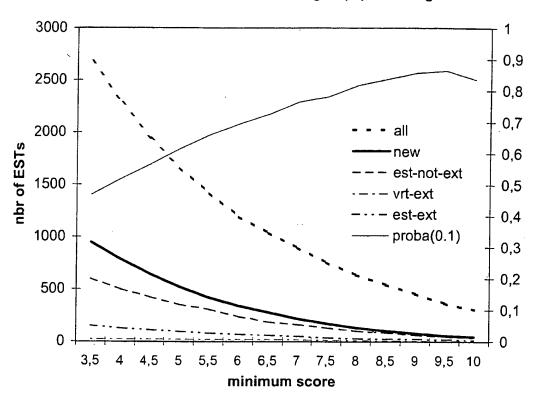


Figure 1

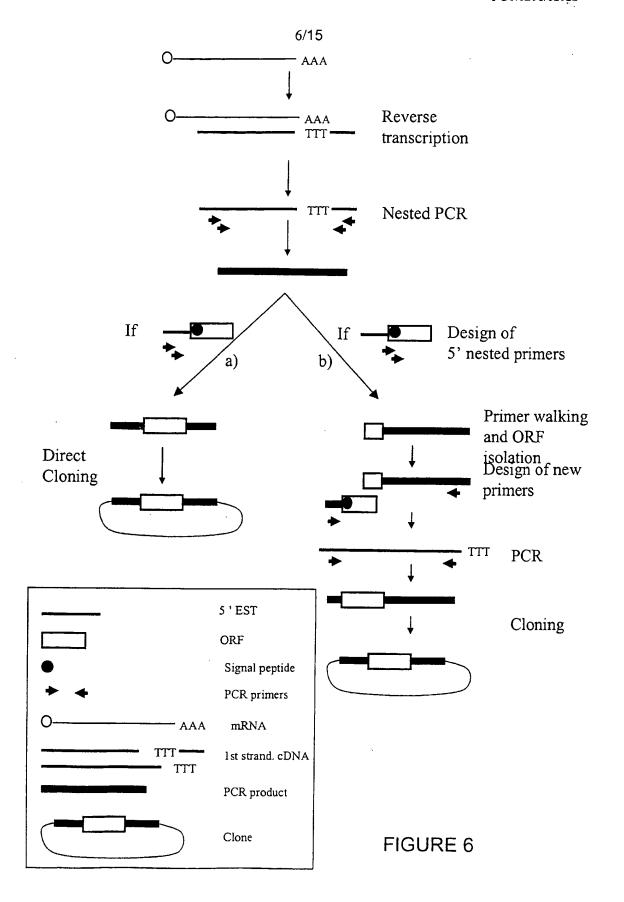
Minimum signal peptide score	false positive rate	false negative rate	proba(0.1)	proba(0.2)
3,5	0,121	0,036	0,467	0,664
4	0,096	0,06	0,519	0,708
4,5	0,078	0,079	0,565	0,745
5	0,062	0,098	0,615	0,782
5,5	0,05	0,127	0,659	0,813
6	0,04	0,163	0,694	0,836
6,5	0,033	0,202	0,725	0,855
7	0,025	0,248	0,763	0,878
7,5	0,021	0,304	0,78	0,889
8	0,015	0,368	0,816	0,909
8,5	0,012	0,418	0,836	0,92
9	0,009	0,512	0,856	0,93
9,5	0,007	0,581	0,863	0,934
10	0,006	0,679	0,835	0,919

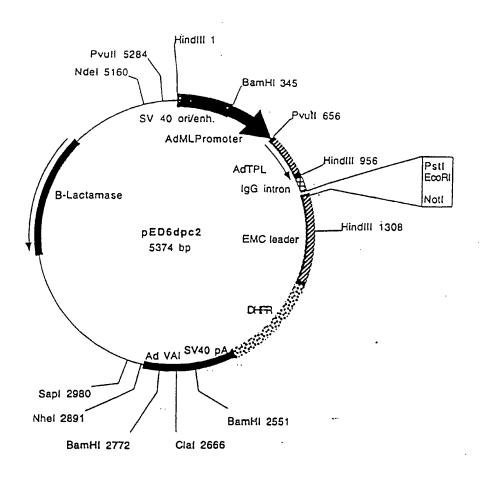
influence of minimum score on signal peptide recognition



Minimum signal peptide score	ĺ	New ESTs	ESTs matching public EST closer than 40 bp from beginning	l known	ESTs extending public EST more than 40 bp
3,5	2674	947	599	23	150
4	2278	784	499	23	126
4,5	1943	647	425	22	112
5	1657	523	353	21	96
5,5	1417	419	307	19	80
6	1190	340	238	18	68
6,5	1035	280	186	18	60
7	893	219	161	15	48
7,5	753	173	132	12	36
8	636	133	101	11	29
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9	456	81	63	6	24
9,5	364	57	48	6	18
10	303	47	35	6	15

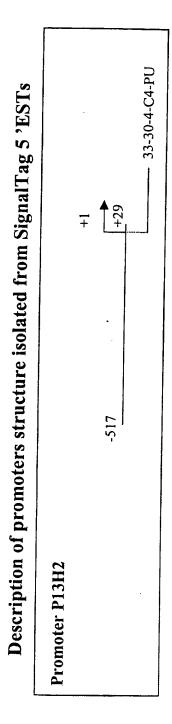
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Brain	329	131	75	3	24
Cancerous prostate	134	40	37	1	6
Cerebellum	17	9	1	0	6
Colon	21	11	4	0	ol
Dystrophic muscle	41	18	8	0	1
Fetal brain	70	37	16	0	1
Fetal kidney	227	116	46	1	19
Fetal liver	13	7	2	0	0.
Heart	30	15	7	0	1
Hypertrophic prostate	86	23	22	2	2
Kidney	10	7	3	0	ō
Large intestine	21	8	4	.0	1
Liver	23	9	6	0	o
Lung	24	12	4	0	. 1
Lung (cells)	57	38	6	0	4
Lymph ganglia	163	60	23	2	12
Lymphocytes	23	6	4	0	2
Muscle	33	16	6	0	4
Normal prostate	181	61	45	7	11
Ovary	90	57	12	1	2
Pancreas	48	11	6	0	1
Placenta	24	5	1	0	0
Prostate	34	16	4	0	2
Spleen	56	28	10	0	2
Substantia nigra	108	47	27	1	6
Surrenals	15	3	3	1	0
Testis	131	68	25	1	
Thyroid	17	8	2	0	8 2 3 2
Umbilical cord	55	17	12	1	3
Uterus	28	15	3	0	2
Non tissue-specific	568	48	177	2	28
Total	2677	947	601	23	150

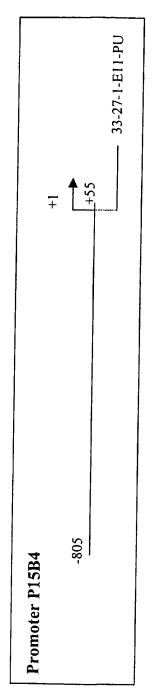




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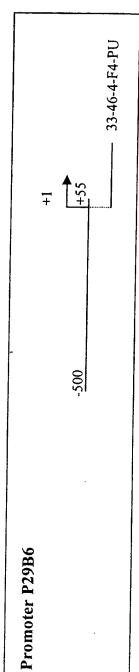


FIGURE 8

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Description of Transcription Factor Binding Sites present on promoters isolated from SignalTag sequences

Pr moter sequence P13H2 (546 bp):

Matrix	Position	Orientation	Score	Length	Sequence
CMYB_01	-502	+	0.983	9	TGTCAGTTG
MYOD_Q6	-501	•,	0.961	10	CCCAACTGAC
S8_01	-444	•	0.960	11	AATAGAATTAG
S8_01	-425	+	0.966	11	AACTAAATTAG
DELTAEF1_01	-390	-	0.960	11	GCACACCTCAG
GATA_C	-364	•	0.964	11	AGATAAATCCA
CMYB_01	-349	+	0.958	9	CTTCAGTTG
GATA1_02	-343	+	0.959	14	TTGTAGATAGGACA
GATA_C	-339	+	0.953	11	AGATAGGACAT
TAL1ALPHAE47_01	-235	+	0.973	16	CATAACAGATGGTAAG
TAL1BETAE47_01	-235	+	0.983	16	CATAACAGATGGTAAG
TAL1BETAITF2_01	-235	+	0.978	16	CATAACAGATGGTAAG
MYOD_Q6	-232	-	0.954	10	ACCATCTGTT
GATA1_04	-217	-	0.953	13	TCAAGATAAAGTA
IK1_01	-126	+	0.963	13	AGTTGGGAATTCC
IK2_01	-126	+	0.985	12	AGTTGGGAATTC
CREL_01	-123	+	0.962	10	TGGGAATTCC
GATA1_02	-96	+	0.950	14	TCAGTGATATGGCA
SRY_02	-41	•	0.951	12	TAAAACAAAACA
E2F_02	-33	+	0.957	8	TTTAGCGC
MZF1_01	-5	•	0.975	8	TGAGGGGA

Promoter sequence P15B4 (861bp):

Matrix	Position	Orientation	Score	Length	Sequence
NFY_Q6	-748	-	0.956	11	GGACCAATCAT
MZF1_01	-738	+	0.962	8	CCTGGGGA
CMYB_01	-684	+	0.994	9	TGACCGTTG
VMYB_02	-682	-	0.985	9	TCCAACGGT
STAT_01	-673	+	0.968	9	TTCCTGGAA
STAT_01	-673	-	0.951	9	TTCCAGGAA
MZF1_01	-556	-	0.956	8	TTGGGGGA
IK2_01	-451	+	0.965	12	GAATGGGATTTC
MZF1_01	-424	+	0.986	8	AGAGGGGA
SRY_02	-398	• •	0.955	12	GAAAACAAAACA
MZF1_01	-216	+	0.960	8	GAAGGGGA
MYOD_Q6	-190	+	0.981	10	AGCATCTGCC
DELTAEF1_01	-176	+	0.958	11	TCCCACCTTCC
S8_01	5	-	0.992	11	GAGGCAATTAT
MZF1_01	16	-	0.986	8	AGAGGGGA

Promoter sequence P29B6 (555 bp):

Matrix	Position	Orientation	Score	Length	Sequence
ARNT_01	-311	+	0.964	16	GGACTCACGTGCTGCT
NMYC_01	-309	+	0.965	12	ACTCACGTGCTG
USF_01	-309	+	0.985	12	ACTCACGTGCTG
USF_01	-309	•	0.985	12	CAGCACGTGAGT
NMYC_01	-309	•	0.956	12	CAGCACGTGAGT
MYCMAX_02	-309	-	0.972	12	CAGCACGTGAGT
USF_C	-307	+	0.997	8	TCACGTGC
USF_C	-307	-	0.991	8	GCACGTGA
MZF1_01	-292	-	0.968	8	CATGGGGA
ELK1_02	-105	+	0.963	14	CTCTCCGGAAGCCT
CETS1P54_01	-102	+	0.974	10	TCCGGAAGCC
AP1_Q4	-42	-	0.963	11	AGTGACTGAAC
AP1FJ_Q2	-42	-	0.961	11	AGTGACTGAAC
PADS_C	45	+	1.000	9	TGTGGTCTC

Figure 9

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100.0% identity in 125 aa overlap SEQ ID NO: 217 MADEELEALRRQRLAELQAKHGDPGDAAQQEAKHREAEMRNSILAQVLDQSARARLSNLA SEQ ID NO: 516 MADEELEALRRQRLAELQAKHGDPGDAAQQEAKHREAEMRNSILAQVLDQSARARLSNLA SEQ ID NO: 217 LVKPEKTKAVENYLIQMARYGQLSEKVSEQGLIEILKKVSQQTEKTTTVKFNRRKVMDSD SEQ ID NO: 516 LVKPEKTKAVENYLIQMARYGQLSEKVSEQGLIEILKKVSQQTEKTTTVKFNRRKVMDSD

SEQ ID NO: 217 EDDDY ::::X
SEQ ID NO: 516 EDDDY

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CLUSTAL W(1.5) multiple sequence alignment

SEQ ID NO: 517 SEQ ID NO: 232 SEQ ID NO: 174 SEQ ID NO: 175	MFCPLKLILLPVLLDYSLGLNDLNVSPPELTVHVGDSALMGCVFQSTEDKCIFKIDWTLS
SEQ ID NO: 517 SEQ ID NO: 232 SEQ ID NO: 174 SEQ ID NO: 175	PGEHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDNLCNDGSLLLQDVQDVE
SEQ ID NO: 517 SEQ ID NO: 232 SEQ ID NO: 174 SEQ ID NO: 175	KGESQVFKKAVVLHVLPEEPKGTQMLTKGESQVFKKAVVLHVLPEEPKELMVHVGGLIQMGCVFQSTEVKHVTKVEWIFSGRRAKEEKGESQVFKKAVVLHVLPEEPKELMVHVGGLIQMGCVFQSTEVKHVTKVEWIFSGRRAK
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SEQ ID NO: 517 SEQ ID NO: 232 SEQ ID NO: 174 SEQ ID NO: 175	LVFKKTIVLHVSPEEPRTLVTPAALRPLVLGGNQLVIIVGIVCATILLLPVLILIVKKTC
SEQ ID NO: 517 SEQ ID NO: 232 SEQ ID NO: 174 SEQ ID NO: 175	GNKSSVNSTVLVKNTKKTNP

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99.6% identity in 225 aa overlap SEQ ID NO: 515 PTAVQKEEARQDVEALLSRTVRTQILTGKELRVATQEKEGSSGRCMLTLLGLSFILAGLI SEQ ID NO: 231 LRVATQEKEGSSGRCMLTLLGLSFILAGLI SEQ ID NO: 515 VGGACIYKYFMPKSTIYRGEMCFFDSEDPANSLRGGEPNFLPVTEEADIREDDNIAIIDV SEQ ID NO: 231 VGGACIYKYFMPKSTIYRGEMCFFDSEDPANSLRGGEPNFLPVTEEADIREDDNIAIIDV SEQ ID NO: 515 PVPSFSDSDPAAIIHDFEKGMTAYLDLLLGNCYLMPLNTSIVMPPKNLVELFGKLASGRY SEQ ID NO: 231 PVPSFSDSDPAAIIHDFEKGMTAYLDLLLGICYLMPLNTSIVMPPKNLVELFGKLASGRY SEQ ID NO: 515 LPQTYVVREDLVAVEEIRDVSNLGIFIYQLCNNRKSFRLRRRDLLLGFNKRAIDKCWKIR SEQ ID NO: 231 LPQTYVVREDLVAVEEIRDVSNLGIFIYQLCNNRKSFRLRRRDLLLGFNKRAIDKCWKIR SEQ ID NO: 515 HFPNEFIVETKICQE ::::::::::::::: SEQ ID NO: 231 HFPNEFIVETKICQE

13/15

99.7% identity in 353 aa overlap SEQ ID NO:196 MERGLKSADPRDGTGYTGWAGIAVLYLHLY SEQ ID NO:518 LAEGYFDAAGRLTPEFSQRLTNKIRELLQQMERGLKSADPRDGTGYTGWAGIAVLYLHLY SEQ ID NO:196 DVFGDPAYLQLAHGYVKQSLNCLTKRSITFLCGDAGPLAVAAVLYHKMNNEKOAEDCITR SEQ ID NO:518 DVFGDPAYLQLAHGYVKQSLNCLTKRSITFLCGDAGPLAVAAVLYHKMNNEKOAEDCITR SEQ ID NO:196 LIHLNKIDPHAPNEMLYGRIGYIYALLFVNKNFGVEKTPQSHIQQICETILTSGENLARK SEQ ID NO:518 LIHLNKIDPHAPNEMLYGRIGYIYALLFVNKNFGVEKIPQSHIQQICETILTSGENLARK SEQ ID NO:196 RNFTAKSPLMYEWYQEYYVGAAHGLAGIYYYLMQPSLQVSQGKLHSLVKPSVDYVCQLKF SEQ ID NO:518 RNFTAKSPLMYEWYQEYYVGAAHGLAGIYYYLMQPSLQVSQGKLHSLVKPSVDYVCQLKF SEQ ID NO:196 PSGNYPPCIGDNRDLLVHWCHGAPGVIYMLIQAYKVFREEKYLCDAYQCADVIWQYGLLK SEQ ID NO:518 PSGNYPPCIGDNRDLLVHWCHGAPGVIYMLIQAYKVFREEKYLCDAYQCADVIWQYGLLK 300~ SEQ ID NO:196 KGYGLCHGSAGNAYAFLTLYNLTQDMKYLYRACKFAEWCLEYGEHGCRTPDTPFSLFEGM SEQ ID NO:518 KGYGLCHGSAGNAYAFLTLYNLTQDMKYLYRACKFAEWCLEYGEHGCRTPDTPFSLFEGM SEQ ID NO:196 AGTIYFLADLLVPTKARFPAFEL SEQ ID NO:518 AGTIYFLADLLVPTKARFPAFEL

SEQ ID NO:158 PP

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98.5% identity in 194 aa overlap 90 100 110 120 SEQ ID NO:519 ARNLPPLTDAQKNKLRHLSVVTLAAKVKCIPYAVLLEALALRNVRQLEDLVIEAVYADVL SEQ ID NO:158 ARNLPPLTEAQKNKLRHLSVVTLAAKVKCIPYAVLLEALALRNVRQLEDLVIEAVYADVL 70 150 160 170 180 190 SEQ ID NO:519 RGSLDQRNQRLEVDYSIGRDIQRQDLSAIAQTLQEWCVGCEVVLSGIEEQVSRANQHKEQ SEQ ID NO:158 RGSLDQRNQRLEVDYSIGRDIQRQDLSAIARTLQEWCVGCEVVLSGIEEQVSRANQHKEQ 130 140 210 220 230 250 SEQ ID NO:519 QLGLKQQIESEVANLKKTIKVTTAAAAAATSQDPEQHLTELREPASGTNQRQPSKKASKG SEQ ID NO:158 QLGLKQQIESEVANLKKTIKVTTAAAAAATSQDPEQHLTELREPAPGTNQRQPSKKASKG 190 200 210 270 SEQ ID NO:519 KGLRGSAKIWSKSN SEQ ID NO:158 KGLRGSAKIWSKSN 240 88.7% identity in 62 aa overlap 20 30 40 SEQ ID NO:519 MSAEVKVTGQNQEQFLLLAKSAKGAALATLIHQVLEAPGVYVFGELLDMPNVRELAESDF SEQ ID NO:158 MSAEVKVTGQNQEQFLLLAKSAKGAALATLIHQVLEAPGVYVFGELLDMPNVRELXARNL 10 20 30 4.0 SEQ ID NO:519 AS

15/15

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			50 70					
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			:::::::	:				
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722

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Ser Pro Cys Leu Thr
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cccggagata ggaccaaccg tcaggaatgc gaggaatgtt tttcttcgga ctctatcgag
                                                                      180
                                                                      231
gcacacagac agacc atg ggg att ctg tct aca gtg aca gcc tta aca ttt
                 Met Gly Ile Leu Ser Thr Val Thr Ala Leu Thr Phe
                                      -10
                                                                      279
gcc ara gcc ctg gac ggc tgc aga aat ggc att gcc cac cct gca agt
Ala Xaa Ala Leu Asp Gly Cys Arg Asn Gly Ile Ala His Pro Ala Ser
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gag aag cac aga ctc gag aaa tgt agg gaa ctc gag asc asc cac tcg
Glu Lys His Arg Leu Glu Lys Cys Arg Glu Leu Glu Xaa Xaa His Ser
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gcc cca gga tca acc cas cac cga aga aaa aca acc aga aga aat tat
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Ala Pro Gly Ser Thr Xaa His Arg Arg Lys Thr Thr Arg Arg Asn Tyr
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                    35
                                        40
                                                                      424
tot toa goo tgaaatgaak cogggatoaa atggttgctg atcaragcco
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Leu Val Leu Thr Leu Cys Thr Leu Pro Leu Ala Val Ala Ser Ala Gly
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tgc gcc acg acg cca gct cgc aac ctg agc tgc tac cag tgc ttc aag
                                                                      153
Cys Ala Thr Thr Pro Ala Arg Asn Leu Ser Cys Tyr Gln Cys Phe Lys
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gtc agc agc tgg acg gag tgc ccg ccc acc tgg tgc agc ccg ctg gac
                                                                      201
Val Ser Ser Trp Thr Glu Cys Pro Pro Thr Trp Cys Ser Pro Leu Asp
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                    25
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Gln Val Cys Ile Ser Asn Glu Val Val Val Ser Phe Lys Trp Ser Val
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cgc gtc ctg ctc agc aaa cgc tgt gct ccc aga tgt ccc aac gac aac
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Arg Val Leu Leu Ser Lys Arg Cys Ala Pro Arg Cys Pro Asn Asp Asn
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agg cgc tgc tgt tcc tgg gct ctc tgc aac agg gca ctg acc cca cag
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Arg Arg Cys Cys Ser Trp Ala Leu Cys Asn Arg Ala Leu Thr Pro Gln
                         90
    85
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Glu Gly Arg Trp Ala Leu Xaa Gly Gly Leu Leu Leu Gln Asp Pro Ser
                     105
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agg ggc ara aaa acc tgg gtg cgg cca cag ctg ggg ctc cca ctc tgc
Arg Gly Xaa Lys Thr Trp Val Arg Pro Gln Leu Gly Leu Pro Leu Cys
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                 120
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ctt ccc awt tcc aac ccc ctc tgc cca rgg gaa acc cag gaa gga
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125 130 135	
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	222
Cys Ile Ile Ile Val Ala Ile Ala Leu Leu Ile Leu Ser Gly Ile Trp 140 145 150	
	580
caa cgt ada ara aag aac aaa gaa cca tct gaa gtg gat gac gct gaa	560
Gln Arg Xaa Xaa Lys Asn Lys Glu Pro Ser Glu Val Asp Asp Ala Glu 155 160 165	
	628
rat aak tgt gaa aac atg atc aca att gaa aat ggc atc ccc tct gat	020
Xaa Xaa Cys Glu Asn Met Ile Thr Ile Glu Asn Gly Ile Pro Ser Asp	
170 175 180 185	CDC
ccc ctg gac atg aag gga ggg cat att aat gat gcc ttc atg aca gag	676
Pro Leu Asp Met Lys Gly Gly His Ile Asn Asp Ala Phe Met Thr Glu	
190 195 200	
gat gag agg ctc acc cct ctc tgaagggctg ttgttctgct tcctcaaraa	727
Asp Glu Arg Leu Thr Pro Leu	
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aat ttt agg ata ttt gaa aga aga tat gga agc aga aaa ttt gca tcc Asn Phe Arg Ile Phe Glu Arg Arg Tyr Gly Ser Arg Lys Phe Ala Ser 50 55 60	288

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		tgg aac aag ctt aaa Trp Asn Lys Leu Lys 45	
Lys Arg Ser		tctgaccca gccagagtc	c aggtttccac 372
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Glu Tyr Lys Lys Glu Gln Ala Ile Asn Arg Ala Gly Ile Val Gln Glu
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Asp Val Gln Pro Pro Gly Leu Lys Val Trp Ser Asp Pro Phe Gly Arg
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52

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Glu Leu Ala Gln His Glu Glu Leu Thr Leu Leu Phe His Gly Thr Leu
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Leu Thr Lys Ala Arg Asn Ser Leu Gly Leu Tyr Gly Arg Thr Ile Glu
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ctc ctg ggg cag gag gtc agc cgg ggc cgg gat gca gcc cag gaa ctt
Leu Leu Gly Gln Glu Val Ser Arg Gly Arg Asp Ala Ala Gln Glu Leu
cgg gca agc ctg ttg gag act cag atg gag gag gat att ctg cag ctg
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Arg Ala Ser Leu Leu Glu Thr Gln Met Glu Glu Asp Ile Leu Gln Leu
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Lys Val Leu Arg Asp Ser Val Gln Arg Leu Glu Val Gln Leu Arg Ser
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-10 -5	
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5 10 15 20	
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Asp 145 ctgu cats aga cttc gaget acaca acca accca accca accca accca accca accca accca accca accca accca a acca acca acca a acca a acca acca a acca acca ac a acca ac a acca a ac a acca a ac a ac a ac a ac a a a ac a a ac a ac a	agg atc catagggt tagt tagt tagt tagt catagggt tagt catagggt tagt cataggggt tagt cataggggt tagt catagggggt tagt catagggggggggg	Leu cag Gln cat His gac gcc gtg gcag gcag gcag gct cat cac	Asp tgg Trp cag Gln lcca tgttttg ttttg ttttg tccae	gct Ala 165 agt ser acag ttaa gatt catc gatt tcctc gaact ttcct tcctc tcc	His oca grant and the case of	gag Glu aaa Lys ggttaa ggttaatggtaatggtaaaggtaatggtaatggttaatggttaatggttaatggttaatggttatttttt	Cly ctg Leu gca Ala tggcat ccatc acttg acttg actgaa gtagaa ctgaa ctgaa ccatc actgaa ccatc actga	gag gag gag aag gaag gag gag gag gag ga	gag Glu 170 tagg agcca taata taacca taccca tacca taccca tacca taccca tacca taccca taccca tacca taccca tacca tacca tacca tacca tacca tac	Ser 155 aat 155 aat 255 act 25	ctc Leu aat caa caa caa ggtg atc caa ctg	ser aat Asn tgtt aagat tcact tccct taacta acgg aaat ttgcct ttgcct tttgct	Ala gag Glu gcgg attat agca gag ttaat aaat aaat ctggt	Glu ctc Leu 175 ga tggat ccctg ccaaa ggatc ccttg gctttg accc tttg gaccc tttg	Leu 160 acc Thr ttgtga gcctgt tccagct ttgtag accagc gtggag ttttc agtctc agtctc agtctc agtctc cagctt cagctt	1013 1060 1120 1180 1240 1300 1420 1480 1600 1660 1720 1780 1840 1900
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                                                                      180
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Thr Asp Gly Leu Ala Ala Ile Asn Leu Leu Lys Trp Ile Lys Thr Leu
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                                    -30
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Leu Tyr Ile Val Cys Arg Cys Gly Ser His Leu Trp Arg Glu Ser His
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His
10
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Lys	Ala	Ser	Leu 35	Glu	Ile	Glu	Tyr	Gln 40	Val	Leu	Asp	Gly	Ala 45	gga Gly	Leu	245
Asp	Ile	Asp 50	Phe	His	Leu	Ala	Ser 55	Pro	Glu	Gly	Lys	Thr 60	Leu	gtt Val	Phe	293
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Thr Gly Val Val Phe Gly Ala Ser Leu Phe Leu Leu Ser Leu Thr.
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Ser Val Thr Ile Ser Phe Arg Ile Tyr Lys Gly Val Ile Gln Ala Ile
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Asp Asp Leu Val Asp Ser Leu Lys Phe Ala Val Leu Met Trp Val Phe
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Met Glu Trp Ala

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-70	_			-	-65	_	•	•	•	-60					-55	
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His	Gln	Val	Leu	Glu	Ala	Pro	Gly	Val	Tyr	Val	Phe	Gly	Glu	Leu	Leu	
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Asp	Met	Pro		Val	Arg	Glu	Leu		Ala	Arg	Asn	Leu	-25	Pro	Leu	
	~~~	aat	-35	226	+	224	a++	-30	~~~	ctc	tca	att		acc	cta	360
aca Th∽	gag	y) a	Cag	Lve	Agn	Lve	T.AII	Ara	His	Len	Ser	Val	Val	acc Thr	Leu	300
TIIL	GIU	-20	GIII	шуъ	ASII	шуз	-15	Ar 9	1110	200	501	-10				
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Ala	Ala	Lys	Val	Lys	Cys	Ile	Pro	Tyr	Āla	Val	Leu	Leu	Glu	Ala	Leu	
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Tyr	Ala	Asp	30	пеп	Arg	Gry	261	35	Азр	GIII	nr 9	A311	40	9	200	
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Glu	Val	Asp	Tyr	Ser	Ile	Gly	Arg	Asp	Ile	Gln	Arg	Gln	Āsp	Leu	Ser	
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Ala	Ile	Ala	Arg	Thr	Leu		Glu	Trp	Cys	Val		Cys	Glu	Val	Val	
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ьеи 75	ser	GIA	тте	GIU	80	GIN	vaı	ser	Arg	85	MSII	GIII	птэ	Lys	90	
	cad	cta	aac	cta		cag	cag	att	gag		gag	att	acc	aac		696
Gln	Gln	Leu	Glv	Leu	Lvs	Gln	Gln	Ile	Glu	Ser	Glu	Val	Ala	Asn	Leu	
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aaa	aaa	acc	att	aaa	gtt	acg	acg	gca	gca	gca	gcc	gca	gcc	aca	tct	744
Lys	Lys	Thr	Ile	Lys	Val	Thr	Thr	Ala	Ala	Ala	Ala	Ala		Thr	Ser	
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Gin	Asp		GIu	GIn	HIS	ьeu	130	GIU	Leu	Arg	GIU	135	Ald	PIO	Gly	
200	220	125	cac	cad	ccc	agc		aaa	acc	tca	aaq		aaq	999	ctc	840
Thr	Asn	Gln	Ara	Gln	Pro	Ser	Lvs	Lvs	Ala	Ser	Lys	Gly	Lys	Gly	Leu	
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Arg	Gly	Ser	Ala	Lys	Ile	Trp	Ser	Lys	Ser	Asn						
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cct	taaq	age	tcaq	catc	ta t	ccct	attc	a tt	acat	gtca	ttq	agta	qgt	gggt	agccct	1193
gat	aaaa	atc	actc	tatc	tg q	agca	taac	с са	cagg	cgtt	ttt	tctg	cca	CCCC	atccct	1253
gca	tgcc	tga	tccc	cagt	tc c	tata	ccct	a cc	cctg	acct	att	gago	agc	ctct	gaagag	1313
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cgt	ttct	taa	catg	ttga	ga g	atga	ctct	t tc	trgg	ccct	ggc	cato	ccg	ggaa	gcttga	1613
tgg	caat	cct tat	ggaa	gggt	ct a	acct	atat	e to	cate	tato	919	yyya atat	ayy	atga	ggtata cgcaga	1673
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                                                                      170
                Met Pro Thr Asn Cys Ala Ala Ala Gly Cys Ala Thr
acc tac aac aag cac att aac atc agc ttc cac agg taacctgggc
                                                                      216
Thr Tyr Asn Lys His Ile Asn Ile Ser Phe His Arg
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                                                                      456
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                                                                      996
ccagtcctga ttttatatat tttatatacc taacaacgta tatgttagta tgtagaaatt
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		Asn														
1111	- y -	15	<b>_</b>	1113	110	Vaii	20	501	1	*****	9	25				
									~+~		~~~	_	222	22t	+++	266
		aga	_		_		_	_	_	-						200
Pro	-	Arg	Arg	гÀг	GIu	_	vaı	Arg	ьeu	vaı	_	Arg	гÀг	Asn	Pne	
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		gga														314
Val	Pro	Gly	Lys	His	Thr	Phe	Leu	Cys	Ser	Lys	His	Phe	Glu	Ala		
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Cys	Phe	Asp	Leu	Thr	Gly	Gln	Thr	Arg	Arg	Leu	Lys	Met	Asp	Ala	Val	
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cca	acc	att	ttt	gat	ttt	tgt	acc	cat	ata	aag	tct	atg	aaa	ctc	aag	410
		Ile														
			80	-		•		85		-			90		-	
tca	agg	aat	-	tta	aaσ	aaa	aac		agt	tat	tct	cca	act	qqa	cca	458
		Asn														
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Ser		Leu	БУБ	261	ASII		SCI	261	GIII	GIII		пец	пси	GIU	1113	
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		gcc														334
	Tyr	Ala	Phe	Arg		Pro	Met	GIu	Ala		rys	Arg	ıте	TTE		
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Gln	Lys	Glu	Arg	Arg	Ala	Thr	Arg	Arg	Trp	Ile	Lys	Ala	Met	Cys	Leu	
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Val	Lvs	Asn	Leu	Glu	Ala	Asn	Ser	Val	Leu	Pro	Lvs	Gly	Thr	Ser	Glu	
	- 4	175					180				-	185				
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Hic	Met	Leu	Dro	Thr	Δla	T.e.ii	Ser	Ser	Leu	Pro	Len	Glu	Asp	Phe	Lvs	
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250		gaa		~~-			~~+		202	ata		aat	cta	aat	cta	794
77-	7	gaa	Caa	gat	Caa	Caa	yat	Tura	mbw	Tou	Ton	Cor	Tou	Acn	T.Au	,,,,
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205					210					215						848
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Lys	Gln	Thr	Lys		Thr	Phe	Iте									
				225												
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															agaata	968
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                            ~50
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Tyr Leu Thr Pro Val Leu Lys Glu Ser Lys Phe Arg Glu Thr Gly Val
                                          -30
                       -35
                                                                     200
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Ile Thr Pro Glu Glu Phe Val Ala Ala Gly Asp His Leu Val His His
                                        -15
                    -20
tgt cca aca tgg caa tgg gct aca ggg gaa gaa ttg aaa gtg aag gca
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Cys Pro Thr Trp Gln Trp Ala Thr Gly Glu Glu Leu Lys Val Lys Ala
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                                                                      296
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Tyr Leu Pro Thr Gly Lys Gln Phe Leu Val Thr Lys Asn Val Pro Cys
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tat aag cgg tgc aaa cag atg gaa tat tca gat gaa ttg gaa gct atc
                                                                      344
Tyr Lys Arg Cys Lys Gln Met Glu Tyr Ser Asp Glu Leu Glu Ala Ile
                        30
                                                                      392
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Ile Glu Glu Asp Asp Gly Asp Gly Gly Trp Val Asp Thr Tyr His Asn
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aca ggt att aca gga ata acg gaa gcc gtt aaa gag atc aca ctg gaa
                                                                      440
Thr Gly Ile Thr Gly Ile Thr Glu Ala Val Lys Glu Ile Thr Leu Glu
                                    65
                                                                      488
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gaa gaa gat gaa gat gaa gga gaa gct gca gat atg gaa gaa tat gaa
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Glu Glu Asp Glu Gly Glu Ala Ala Asp Met Glu Glu Tyr Glu
                            95
                                                                      584
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Glu Ser Gly Leu Leu Glu Thr Asp Glu Ala Thr Leu Asp Thr Arg Lys
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                        110
ata gta gaa gct tgt aaa gcc aaa act gat gct ggc ggt gaa gat gct
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Ile Val Glu Ala Cys Lys Ala Lys Thr Asp Ala Gly Glu Asp Ala
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                    125
att ttg caa acc aga act tat gac ctt tac atc act tat gat aaa tat
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Tac	cag	mb _x	Dro	Arg	Lua	TTT	Len	Dhe	99°	Tyr	Aen	Glu	Gln	Ara	Gln		
Tyr	GIII	TIII		Arg	Бец	пр	Бец	160	Gry	+ y -	нар	Olu	165	AL 9	0111		
			155	~~~		- t-a	+ - +		~~~	ata	aat	C 2 C		cat	ata	77	6
CCT	tta -	aca	gtt	gag	cac	alg	man	gaa	yac	TIA	cor	Cay	yat Nan	uic	yal		•
Pro	Leu		vaı	Glu	HIS	Met		GIU	Asp	TIE	ser		Asp	птъ	vai		
		170					175					180				82	4
aag	aaa	aca	gtg	acc	att	gaa	aat	cat	CCT	cat	ccg	CCa	CCa	D	Dwo	02	-
Lys	_	Thr	Val	Thr	He		Asn	HIS	Pro	HIS		Pro	Pro	PIO	PIO		
	185					190					195					0.7	_
atg	tgt	tca	gtt	cac	cca	tgc	agg	cat	gct	gag	gtg	atg	aag	aaa	atc	87	2
Met	Cys	Ser	Val	His		Cys	Arg	His	Ala		Val	Met	Lys	ьуs			
200					205					210					215		
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Ala Pro Leu Gln Phe Met Ala Ser Ala Leu Phe Ile Trp Ala Ala His
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ctctataaaa ttgggaaatt atctaagatc attttcccta agcattgaca catagcttca
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tgc cgg aag tac tac ctg ggg ggg ttt gct ttc ttg cct ttt ctc tgg Cys Arg Lys Tyr Tyr Leu Gly Gly Phe Ala Phe Leu Pro Phe Leu Trp -55 -50 -45	158
ttg gtc aac atc ttc tgg ttc tac cga gag gcc ttc ctt gtc cca gcc Leu Val Asn Ile Phe Trp Phe Tyr Arg Glu Ala Phe Leu Val Pro Ala	206
tac aca gaa cag agc caa atc aaa ggc tat gtc tgg cgc tca gct gtg Tyr Thr Glu Gln Ser Gln Ile Lys Gly Tyr Val Trp Arg Ser Ala Val	254
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cag atc tac egg ecc ege tgg ggt gee ett ggg gac tac etc tee tte Gln Ile Tyr Arg Pro Arg Trp Gly Ala Leu Gly Asp Tyr Leu Ser Phe	350
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	Arg -35					-30					-25					
gct Ala -20	tca Ser	gcc Ala	cgc Arg	ggc Gly	aag Lys -15	gag Glu	ctg Leu	cgc Arg	ctg Leu	ata Ile -10	ctg Leu	agc Ser	cct Pro	ctg Leu	ect Pro -5	193
Gly	gcc Ala	Gln	Pro	Gln 1	Gln	Glu	Pro	Leu 5	Ala	Leu	Val	Phe	Arg 10	Phe	Gly	241
Met	tcc Ser	Gly 15	Ser	Phe	Gln	Leu	Val 20	Pro	Arg	Glu	Glu	Leu 25	Pro	Arg	His	289
gcc Ala	cac His 30	ctg Leu	cgc Arg	ttt Phe	tac Tyr	acg Thr 35	gcc Ala	ccg Pro	cct Pro	ggc Gly	ccc Pro 40	cgg Arg	ctc Leu	gcc Ala	cta Leu	337
tgt Cys 45	ttc Phe	gtg Val	gac Asp	atc Ile	cgc Arg 50	cgg Arg	ttc Phe	ggc Gly	cgc Arg	tgg Trp 55	gac Asp	ctt Leu	ggg Gly	gga Gly	aag Lys 60	385
tgg Trp	cag Gln	ccg Pro	ggc Gly	cgc Arg 65	999 Gly	ccc Pro	tgt Cys	gtc Val	ttg Leu 70	cag Gln	gag Glu	tac Tyr	cag Gln	cag Gln 75	ttc Phe	433
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atc Ile	tgc Cys	gag Glu 95	gcc	ctc Leu	ctg Leu	gac Asp	cag Gln 100	agg Arg	ttc Phe	ttc Phe	aat Asn	ggc Gly 105	att Ile	ggc Gly	aac Asn	529
tat Tyr	ctg Leu 110	cgg	gca Ala	gag Glu	atc Ile	ctg Leu 115	tac	cgg Arg	ctg Leu	aag Lys	atc Ile 120	ccc Pro	ccc Pro	ttt Phe	gag Glu	577
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ctg Leu	ctg Leu	gag Glu	cta Leu 160	tgt	cac His	tca Ser	gtg Val	ccc Pro 165	aag	gaa Glu	gtg Val	gtc Val	cag Gln 170	ttg Leu	ggt Gly	721
gag Glu	gcc Ala	aaa Lys 175	gat	ggc Gly	agc Ser	aac Asn	ctc Leu 180	tgc	ttc Phe	agc Ser	aaa Lys	tga	ttgt	gta		767
acc	ctaa		actt	atcc	cc c	tcta		t qa	ttca	ccqa	ttt	ggaa	gtt	tgta	gcccta	827
qct	qata	ctc	aatq	gact	ag q	cctc	ctca	c tt	gtca	atag	tgt	ttcc	agg	ctgg	gcgcag	887
tgg	ctca	tgc	ctgt	ggtc	cc g	gcac	ttcg	g ga	ggcc	gagt	999	gtgg	ctc	acct	gaggtc	947
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195

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Asp Ala Leu Pro Pro Ser Lys Ala Pro Ser Lys Thr Arg Arg Ala Lys 205 210 215	٠.
aga gac ctt ggt aag agg act gga acc cag cgg cct gag ggg acc agc	913
Arg Asp Leu Pro Lys Arg Thr Ala Thr Gln Arg Pro Glu Gly Thr Ser 225 230 235	041
ctc cag cag gac cca gaa gct ccc aca gtg ccc aag aag ggg agg agg Leu Gln Gln Asp Pro Glu Ala Pro Thr Val Pro Lys Lys Gly Arg Arg	961
240 245 250	1009
aag ggg cga cag gca gcc tct ggc cac tgc aga ccc cgg aag gtc aag Lys Gly Arg Gln Ala Ala Ser Gly His Cys Arg Pro Arg Lys Val Lys 255 260 265	1003
gct gac atc cca tcc ttg gaa cca gag ggg acc tca gcc tct Ala Asp Ile Pro Ser Leu Glu Pro Glu Gly Thr Ser Ala Ser	1051
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gatetgaatt titgggagea ggeaatatet gaaggtgeaa acaggeeeta eggetgilee	1171 1231
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-50 -45 -40	145
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-35 -30 -25	193
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Met Ser Gly Ser Phe Gln Leu Val Pro Arg Glu Glu Leu Pro Arg His	
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	Gln															133
115	01	110	O ₁	65	Cry	110	Cys	Val	70	GIII	Olu	+ y -	<b>Q1</b> 11	75	1110	
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	gag															401
Arg	Glu	ASII		ьец	Arg	ASII	ьeu		ASP	ьуѕ	ALG	Pne	_	Arg	PIO	
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IIe	Cys		Ala	ьец	ьeu	Asp		Arg	Pne	Pne	Asn	_	TTE	GIY	Asn	
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Tyr	Leu	Arg	Ala	Glu	Ile	Leu	Tyr	Arg	Leu	Lys	Ile	Pro	Pro	Phe	Glu	
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Glu	Leu	Thr	Leu	Ser	Gln	Lys	Ile	Arg	Thr	Lys	Leu	Gln	Asn	Pro	Asp	
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	Leu															
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	Arg															
1	5	175	-1-	1			180	1				185				
cga	gcc	_	cta	cac	tac	tat		atci	cca	aac	ato	_	tcc	cta	cág	817
	Ala										_	_				• -
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	CCC			_	_		_		_			_	_		_	913
Ala	Pro	пуъ	GIA	_	пуъ	261	Arg	пуъ	-	цуб	261	пур	ATG		GIII	
~-~				225					230					235		061
	agt															961
Leu	Ser	PIO		Asp	Arg	vai	GIU		Ala	Leu	Pro	Pro		ьуѕ	Ala	
			240					245					250			1000
	tcc															1009
Pro	Ser		Thr	Arg	Arg	Ala		Arg	Asp	Leu	Pro	_	Arg	Thr	Ala	
		255					260					265				
	cag															1057
Thr	Gln	Arg	Pro	Glu	Gly		Ser	Leu	Gln	Gln	_	Pro	Glu	Ala	Pro	
	270					275					280					
aca							200	aaa	aaa	CCS	cag	CCS	acc	tct	ggc	1105
	gtg															
Thr	gtg Val															
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Thr 285 cac	Val tgc	Pro aga	Lys	Lys cgg	Gly 290 aag	Arg gtc	Arg aag	Lys gct	Gly gac	Arg 295 atc	Gln cca	Ala tcc	Ala ttg	Ser gaa	Gly 300 cca	1153
Thr 285 cac His	Val tgc	Pro aga Arg	Lys ccc Pro	Lys cgg Arg 305	Gly 290 aag Lys	Arg gtc Val	Arg aag Lys	Lys gct Ala	Gly gac Asp 310	Arg 295 atc Ile	Gln cca Pro	Ala tcc Ser	Ala ttg Leu	Ser gaa Glu 315	Gly 300 cca	1153
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Thr 285 cac His gag Glu ccti	tgc Cys ggg Gly	aga Arg acc Thr	Lys ccc Pro tca Ser 320 cgtct	cgg Arg 305 gcc Ala	Gly 290 aag Lys tct Ser	gtc Val tago	aag Lys agga	Lys gct Ala agg o	gac Asp 310 etcto	Arg 295 atc Ile cctto	Gln cca Pro gc tt	Ala tcc Ser cgcac	Ala ttg Leu ctcac	gaa Glu 315	Gly 300 cca Pro	1201
Thr 285 cac His gag Glu ccti gaag	tgc Cys ggg Gly	aga Arg acc Thr	Lys ccc Pro tca Ser 320 cgtct	cgg Arg 305 gcc Ala	Gly 290 aag Lys tct Ser	gtc Val tago	aag Lys agga	Lys gct Ala agg o	gac Asp 310 etcto	Arg 295 atc Ile cctto	Gln cca Pro gc tt	Ala tcc Ser cgcac	Ala ttg Leu ctcac	gaa Glu 315	Gly 300 cca Pro	1201 1261 1321

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Cys Ala Val Val Leu Ala Gln Tyr Leu Trp Phe His Arg Arg Ser Leu
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Pro Gly Lys Ala Ile Leu Glu Ile Gly Ala Gly Val Ser Leu Pro Gly
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Ile Leu Thr Ala Lys Cys Gly Ala Glu Val Ile Leu Ser Asp Ser Ser
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                                        -35
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Glu Leu Pro His Cys Leu Glu Val Cys Arg Gln Ser Cys Gln Met Asn
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                                    -20
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Asn Leu Pro His Leu Gln Val Val Gly Leu Thr Trp Gly His Ile Ser
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Trp Asp Leu Leu Ala Leu Pro Pro Gln Asp Ile Ile Leu Ala Ser Asp
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Val Phe Phe Glu Pro Glu Asp Phe Glu Asp Ile Leu Ala Thr Ile Tyr
                                        30
                    25
                                                                      440
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Phe Leu Met His Lys Asn Pro Lys Val Gln Leu Trp Ser Thr Tyr Gln
                40
                                    45
gtt agg agt gct gac tgg tca ctt gaa gct tta ctc tac aaa tgg gat
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Val Arg Ser Ala Asp Trp Ser Leu Glu Ala Leu Leu Tyr Lys Trp Asp
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atg aaa tgt gtc cac att cct ctt gag tct ttt gat gca gac aaa gaa
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Met Lys Cys Val His Ile Pro Leu Glu Ser Phe Asp Ala Asp Lys Glu
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Val Ile Ser Phe Ala Lys Asp Ser Leu
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tac tat tac Tyr Tyr Tyr -200	Ser Asn Le	c agt gtg		ggg cgc t			05
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Val Glu Trp Ile Phe Ser Gly Arg Arg Ala Lys Val Thr Arg Arg Lys 130 135 140	
cat cac tgt gtt aga gaa ggc tct ggc tgatggtatc aggacaaagg	540
His His Cys Val Arg Glu Gly Ser Gly 145 150	
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Cys Cys Ala Ala Trp Cys Asp Pro Arg Arg Ile His Ser Gln Asp Asp
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Pro Ser Ala Glu Arg Leu Glu Asn Gln Pro Gly Lys Leu Ser Trp Arg
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Leu Cys Ile His His Cys Ser Cys Phe Gln Lys 25 30	Cys Glu Thr Asn Lys 35	
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Ala Pro Gly Thr Ile Pro Glu Leu Pro Thr Phe His Thr Glu Val Ala
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cay any got aga the got are the against the first and the control and the cont	
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Gly Ile Tyr Tyr Leu Met Gln Pro Ser Leu Gln Val Ser Gln Gly	
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Lys Leu His Ser Leu Val Lys Pro Ser Val Asp Tyr Val Cys Gln Leu	
160 165 170	
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Lys Phe Pro Ser Gly Asn Tyr Pro Pro Cys Ile Gly Asp Asn Arg Asp	
175 180 185 190	
ctg ctt gtc cat tgg tgc cat ggc gcc cct ggg gta atc tac atg ctc	777
Leu Leu Val His Trp Cys His Gly Ala Pro Gly Val Ile Tyr Met Leu	
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Ile Gln Ala Tyr Lys Val Phe Arg Glu Glu Lys Tyr Leu Cys Asp Ala	
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Tyr Gln Cys Ala Asp Val Ile Trp Gln Tyr Gly Leu Leu Lys Lys Gly	
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Tyr Gly Leu Cys His Gly Ser Ala Gly Asn Ala Tyr Ala Phe Leu Thr	
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Pro Arg Trp His Arg Leu Pro Pro Gln Ser Leu Gln His His Gln Tyr
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Cys Gln Arg Arg Trp Pro Asp Arg Arg Cys Leu Gln Ser His Thr Gln
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Ser Ser Gly His Leu Pro
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                                                                        99
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             - 5
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                                                                       147
 Arg Glu Ile Lys Lys Gln Leu Leu Leu Ile Ala Gly Leu Thr Arg Glu
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30

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60 65 70	
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Phe Asp Val Lys Glu Tyr Asp Arg Ala Ala His Phe Leu His Gly Cys	
75 80 85	
· · · · · · · · · · · · · · · · · · ·	387
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Asn Ser Lys Lys Ala Tyr Phe Leu Tyr Met Tyr Ser Arg Tyr Leu Val	
90 95 100	425
agg gcc att tta aaa tgt cat tct gcc ttt agt gaa aca tcc ata ttt	435
Arg Ala Ile Leu Lys Cys His Ser Ala Phe Ser Glu Thr Ser Ile Phe	
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Arg Thr Asn Gly Lys Val Lys Ser Phe Lys	
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cac His	att Ile 100	ctg Leu	gcc Ala	ggt Gly	atc Ile	tgc Cys 105	Gly 999	atg Met	gtg Val	gcc Ala	atc Ile 110	tcc Ser	tgg Trp	tac Tyr	gcc Ala	436
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Met Gly Ser Leu Ser Gly

1 5

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Ser	Ser	Tyr 105	Leu	Met	Ile	Ăla	Leu 110	Thr	Val	Val	Gly	Cys 115	Ile	Phe	Met	
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Val	Ile	Glu	Gly	Lys	Lys	Ala 125	Ala	Gln	Arg	His	Glu 130	Thr	Leu	Thr	Ser	
	120		~			_	cat	ata	222	<b>C2C</b>		aca	act	ato	aad	485
ttg	aac	Tan	gaa	aay	Tira	y) a	720	Lou	Lare	Glu	Glu	λla	λ) =	atg Met	Lvs	103
	Asn	Leu	GIU	ьys		Ala	Arg	Бец	пÀè	145	GIU	AIG	Ата	Mec	150	
135					140			~+ ~++	~ ~				+ .	7020	130	537
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	Lys			<b>.</b>						. ~ ~ +		. ~~ ~ +		. + + + .		597
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								gu		Lyc	cyca	iyaas	yea s	Jaaat	aaatt	685
ttet	taaa	idd c	iddac	laaac	id do	aaaa	iaa									003
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						var (	_ys (			cys (	eru 1	ys i		Leu (	эту	
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														acc		20
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gaa	agt	ggt	gga	aga	aag	ctg	aat	aaa	aat	aaa	gct	ttg	act	tca	aaa	146
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Lys	gca Ala 45	30 aga Arg	Phe	Asp	Pro	Tyr 50	gga Gly	Lys	Asn	Lys	Phe 55	tcc Ser	Thr	tgt Cys	aga Arg	
Lys att	gca Ala 45 tgt	30 aga Arg	Phe agt	Asp tct	Pro gtg	Tyr 50 cac	gga Gly caa	Lys	Asn ggt	Lys	Phe 55 cat	tcc Ser	Thr tgc	tgt Cys cag	aga Arg ggc	194 242
Lys att	gca Ala 45 tgt	30 aga Arg	Phe agt	Asp tct	Pro gtg	Tyr 50 cac	gga Gly caa	Lys	Asn ggt	Lys tct Ser	Phe 55 cat	tcc Ser	Thr tgc	tgt Cys	aga Arg ggc Gly	
Lys att Ile <b>6</b> 0	gca Ala 45 tgt Cys	30 aga Arg aaa Lys	Phe agt Ser	Asp tct Ser	Pro gtg Val 65	Tyr 50 cac His	gga Gly caa Gln	Lys cca Pro	Asn ggt Gly	Lys tct Ser 70	Phe 55 cat His	tcc Ser tac Tyr	Thr tgc Cys	tgt Cys cag	aga Arg ggc Gly 75	

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Cys Ala Tyr Lys Lys Gly Ile Cys Ala Met Cys Gly Lys Lys Val Leu	
80 85 90 gat acc aaa aac tac aag caa aca tct gtc tagatgtatt gatggaattt Asp Thr Lys Asn Tyr Lys Gln Thr Ser Val 95 100	340
ctggctttct aaatgatttt actttctgcc ttgaattttc aaggcataga tgtcaactta cagaataaca tgttttaaga taattaagtt taaaccagag aatttgattg ttactcattt tgctctcatg ttctaaacag caacagtgta actagtcttt tgttgtaaat ggttattttc cttataagaa ttttaagaac taaaaaaaaa aaaa	400 460 520 554
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Ser Thr Ser Pro Lys Pro Pro His Thr Leu Ser Arg Lys Gln Trp Arg	
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Asn Arg Gln Lys Asn Lys Arg Arg Cys Lys Asn Lys Phe Gln Pro Pro	005
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Gln Val Pro Asp Gln Ala Pro Ala Glu Ala Pro Thr Glu Lys Thr Glu	
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Phe Gln Glu Asp Pro Glu Ala Phe Leu Leu Tyr His Arg Gly Phe Gln	
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Leu Lys Pro Gly Gly Leu Leu Lys Val Ala Glu Val Ser Ser Arg Phe	1201
360 365 370 375	
gag gat gtt cga acc ttt ctg cgg gct gtg acc aag cta ggc ttc aag	1309
Glu Asp Val Arg Thr Phe Leu Arg Ala Val Thr Lys Leu Gly Phe Lys	
380 385 390 att gtc tcc aag gac ctg acc aac agc cat ttc ttc ttg ttt gat ttc	13,57
Ile Val Ser Lys Asp Leu Thr Asn Ser His Phe Phe Leu Phe Asp Phe	172,
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ggg gcg gcc ggc ttc aca cct tcc ctc gat agc gac ttc acc ttt acc Gly Ala Ala Gly Phe Thr Pro Ser Leu Asp Ser Asp Phe Thr Phe Thr 1 5 10 15	148
ctt ccc gcc ggc cag aag gag tgc ttc tac cag ccc atg ccc ctg aag Leu Pro Ala Gly Gln Lys Glu Cys Phe Tyr Gln Pro Met Pro Leu Lys 20 25 30	196
gcc tcg ctg gag atc gag tac caa gtt tta gat gga gca gga tta gat Ala Ser Leu Glu Ile Glu Tyr Gln Val Leu Asp Gly Ala Gly Leu Asp 35 40	244
att gat ttc cat ctt gcc tct cca gaa ggc aaa acc tta gtt ttt gaa  Ile Asp Phe His Leu Ala Ser Pro Glu Gly Lys Thr Leu Val Phe Glu  50 55 60	292
caa aga aaa tca gat gga gtt cac act gta gag act gaa gtt ggt gat Gln Arg Lys Ser Asp Gly Val His Thr Val Glu Thr Glu Val Gly Asp 65 70 75 80	340
tac atg ttc tgc ttt gac aat aca ttc agc acc att tct gag aag gtg Tyr Met Phe Cys Phe Asp Asn Thr Phe Ser Thr Ile Ser Glu Lys Val 85 90 95	388
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aaa ctg gaa gac atc ctg gaa tcc atc agc agc atc aag tcc aga cta Lys Leu Glu Asp Ile Leu Glu Ser Ile Ser Ser Ile Lys Ser Arg Leu 130 135 140	532
agc aaa agt ggg cac ata caa att ctg ctt aga gca ttt gaa gct cgt Ser Lys Ser Gly His Ile Gln Ile Leu Leu Arg Ala Phe Glu Ala Arg 145 150 155 160	580
gat cga aac ata caa gaa agc aac ttt gat aga gtc aat ttc tgg tct Asp Arg Asn Ile Gln Glu Ser Asn Phe Asp Arg Val Asn Phe Trp Ser 165 170 175	628
atg gtt aat tta gtg gtc atg gtg gtg gtg tca gcc att caa gtt tat  Met Val Asn Leu Val Val Met Val Val Val Ser Ala Ile Gln Val Tyr  180 185 190	676
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<223> Von Heijne matrix

## -86-WO 99/31236 PCT/IB98/02122 -

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<222> 775..787

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													gct Ala			148	l
													agg Arg 1			196	i
													gtg Val			244	:
													aat Asn			292	!
aag Lys	gag Glu	aag Lys	ctg Leu	ctg Leu 40	gca Ala	gaa Glu	gct Ala	gga Gly	atg Met 45	cct Pro	tct Ser	cca Pro	gaa Glu	tgg Trp 50	acc Thr	340	)
													act Thr 65			388	1
_	-	_	_		_	_	-	_				_	gga Gly			436	;
_	_		_	_	_				_				gcc Ala		_	484	;
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	мес	тте		HIS	vai	Tut	ьeu		Asp	Ald	шец	361	-80	Val	ADP	
			-90					-85						~~~	act	96
ctg	ctt	gaa	gag	CTT	CCC	CTC	CCC	gac	cag	cag	CCa	cgc	TIA	gay	Dwo	90
Leu	Leu		Glu	Leu	Pro	Leu		Asp	GIn	GIn	Pro		ıте	GIU	PIO	
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cca	cct	tcc	tcc	atc	atg	tac	cag	gct	aac	ttt	gac	aca	aac	ttt	gag	144
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Val	Clu	Val	Leu	Glu	Pro	Glu	Val	Thr	Lvs	Leu	Met	Lvs	Phe	Met	Tyr	
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-1	cag	cgc	aag	gcc	all	gag	299	Db -	Con	Com	gag Cl.	9.9	Tura	722	Len	
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Thr	Leu	Glv	Lys	Phe	Ile	Asn	Met	Phe	Ala	Val	Leu	Asp	Glu	Leu	Lys	
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Aen	Met	Live	Cys	Ser	Val	Lve	Asn	Asp	His	Ser	Ala	Tvr	Lvs	Ara	Ala	
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Gln	Asn	Leu	Ser	Met	Phe	Leu	Ala	Asn	His	Asn	Arg	Ile	Thr	Gln	Cys	
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rsb	116		Hall	116	Cys	val		* y *	- y -	- Lu	1.011	160		- 1 -		
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Trp Trp Leu Val Gln Ala Val Cys Ile Ala Leu Met Ala Val Ile Gly
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gtc Val 10	ccg Pro	-5 ccc Pro	cca Pro	aaa Lys	cga Arg 15	tc: Ser	l cgc Arg	age g Se:	c aa r Ly:	a cto s Leu 20	ate	g gca t Ala	a cc	g cc	c cga o Arg 25	147

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Ser His Ser Arg Leu Ser Pro Arg Lys Thr His Leu Leu Tyr Ile Leu 160 165 170 175	734
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Ser Thr
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Gln Gly 255	His	Gln	Leu	Phe	His 260	Ile	Phe	Leu	Val	Leu 265	Cys	Thr	Leu	Ala		
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Gln Leu	Glu	Ala	Val		Leu	Asp	Tyr	Glu	Ala 280	Arg	Arg	Pro	Ile	Tyr 285		
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Glu Pro	Leu	His	Thr	His	Trp	Pro	His	Asn	Phe	Ser	Gly	Leu	Phe 300	Leu		
ctc acg	ata		290	age	atc	ctc	act	295 aca	ttc	ctc	ctq	aqc	_	ctg	1065	5
Leu Thr	Val	Gly	Ser	Ser	Ile	Leu	Thr	Ala	Phe	Leu	Leu	Ser	Gln	Leu		
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gta cag	cgc	aaa	ctt	gat	cag	aag	acc	aag	tgaa	agggg	gga 1	tggc.	atct	99	1115	•
Val Gln	Arg	ьys	ьeu	ASP	GIN	шуs 325	THE	пур								
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Phe Val	l Ile	Ala	Cys	Val	Leu	Ser	Leu	Ile	Ser	Thr	Ile	туг	Met	Ala		
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gct tco Ala Se	c att	ggc	aca	gac	ttc Dhe	Trn	tat Tur	gag Glu	tat	. cga	. agt	. cca	val	. Gln	12	
Ala Se	r 116	: GTÀ	THE	Asp	FIIC	111	TYL	JIU	15	1·9	, ,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,			20		
qaa aa	t tcc	agt	gat	ttg	aat	aaa	agc	ato	tgg	gat	gaa	tto	att	agt	19	8
Glu As:	n Ser	Ser	Asp	Leu	Asn	Lys	Ser	Ile	Trp	Asp	Glu	Phe	: Ile 35	Ser		
gat ga	a aaa	ne+	25 gaa	220	act	tat	aat	30 gat	aca	ctt	. ttt	. caa		aat	24	6
Asp Gl	y yea u Ala	. yar Asp	Glu	Lys	Thr	Tyr	Asn	Asp	Ala	Leu	Phe	Arg	туі	Asn		
· <u>-</u>		40		-		-	45	-				50				
1.5p GI	w 43.10			. .		-1-		F					. -			

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ant too tal	age cea	cca qaa	agg aca	gag to	ca ttt	gat gtg	gtc		42
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Lys Cys Va	g age ce	Thr Leu	Thr Glu	Gln P	he Met	Glu Ly	Phe	Val	
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Asp Pro GI			Giy iic	110			115		
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	Leu	Gly	Leu	Met		Val	Val	Thr	Gly		Glu	Asp	Glu	Asn	Ser		
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						Leu										140	,
	•		10					15		•			20	- 2			
_						cca	-						_	_	-	194	ŀ
Gly	Leu		Val	Phe	Tyr	Pro		Leu	Gly	Asn	Ile	-	Cys	Lys	Val		
~++	aat	25	+~+	222		+	30	a a	220	2+4		35	+ ~~		~~~	242	,
_		_	_			tac Tyr	_		_					_		242	•
	40	F	-,-			45	5	•	-1-		50						
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	Ile	Val	Lys	Phe		Gly	Ala	Val	Asp	-	Ala	Thr	Tyr	Ile			
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_	_		-		_	gcc Ala		_	_	_	_		_	_	_	338	5
			p	75	vob		110	561	80	ALU	OIU	110	7.9	85	Ar 9		
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בינים	OI,	105	110	0111	Cly	ÇIII	110	DCu.	JUL	YIG	TYT	115	ATO	FIG	DCI		
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Pro		Ala	His	Ser	Gly	Phe	His	Arg	Tyr	Gln		Phe	Val	Tyr	Leu		
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Leu Pro Asp Glu Ala Arg Ser Leu Pro Pro Pro Lys Leu Thr Asp Pro
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Leu Gly Leu Ser Phe Ile Leu Ala Gly Leu Ile Val Gly Gly Ala Cys	
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Ile Tyr Lys Tyr Phe Met Pro Lys Ser Thr Ile Tyr Arg Gly Glu Met 10 15 20	133
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Cys Phe Phe Asp Ser Glu Asp Pro Ala Asn Ser Leu Arg Gly Glu 25 30 35	
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Val Met Pro Pro Lys Asn Leu Val Glu Leu Phe Gly Lys Leu Ala Ser 105 110 115	
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65 70 75 80	
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Ala His Ile Gly Asp Val Met Phe Thr Gly Thr Ala Asp Gly Arg Val 50 60	

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Lys	Gly		Phe	Glu	Val	Asn		Trp	Lys	Arg	Glu		Lys	Leu	Leu	
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Leu		Ser	Glu	Thr	Pro		GIu	GIY	ьуs	Asn		Ser	Phe	vaı	Asn	
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			tgg													697
ser	ser	ьys	Trp	165	Arg	Arg	Asp	TAL	170	ьeu	Leu	vaı	мес	175	GIY	
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			Gly													745
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            -20
                                -15
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gat gct gtg aag agt aaa atg gat cct gag ctt gaa aaa aaa ctg aaa
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Asp Ala Val Lys Ser Lys Met Asp Pro Glu Leu Glu Lys Lys Leu Lys
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Lys Phe Asp Asp Trp Lys Asn Ile Arg Gly Pro Arg Pro Trp Glu Asp
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Pro Asp Leu Leu Gln Gly Arg Asn Pro Glu Ser Leu Lys Thr Lys Thr
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gcc tcc att ggc aca gac ttc tgg tat gaa tat cga agt cca gtt caa Ala Ser Ile Gly Thr Asp Phe Trp Tyr Glu Tyr Arg Ser Pro Val Gln	150
5 10 15 20	
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Glu Asn Ser Ser Asp Leu Asn Lys Ser Ile Trp Asp Glu Phe Ile Ser 25 30 35	
gat gag gca gat gaa aag act tat aat gat gca ctt ttt cga tac aat	246
Asp Glu Ala Asp Glu Lys Thr Tyr Asn Asp Ala Leu Phe Arg Tyr Asn 40 45 50	
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Gly Thr Val Gly Leu Trp Gly Arg Cys Ile Thr Ile Pro Lys Asn Met	
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His Trp Tyr Ser Pro Pro Glu Arg Thr Gly Ile Ser Leu Ile Leu Thr	746

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Ser Arg Val Met Ser Glu Lys Asp Glu Tyr Gln	ttt caa cat can nna 105 Phe Gln His Xaa Xaa
Ser Arg Val Met Ser Glu Lys Asp Glu Tyr Gln: -30 -25	ttt caa cat can nna 105 Phe Gln His Xaa Xaa -20
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                                              20
Ser Leu Gly Leu Ser Asn Leu Gln Lys Ser Gln Ile Gln Gly Lys Xaa
                       30
Ala Gly Leu Gln Ser Ser Gly Lys Glu Ala Ala Leu Asn Leu Ser Phe
                   45
Ile Ser Lys Glu Glu Met Lys Asn Thr Ser Trp Ile Arg Lys Asn Trp
                                   65
Leu Leu Val Ala Gly Ile Ser Phe Ile Gly Asp His Leu Gly Thr Tyr
                               80
Phe Leu Gln Arg Ser Ala Lys Gln Ser Val Lys Phe Gln Ser Glñ Ser
Lys Gln Lys Ser Ile Glu Glu
  105
```

<210> 146 <211> 255 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -70..-1

<400> 146

Met Gln Gln Lys Glu Gln Gln Phe Arg Glu Trp Phe Leu Lys Glu Phe -65 -60 Pro Gln Ile Arg Trp Lys Ile Gln Glu Ser Ile Glu Arg Leu Arg Val -50 -45 Ile Ala Asn Glu Ile Glu Lys Val His Arg Gly Cys Val Ile Ala Asn -25 -35 -30 Val Val Ser Gly Ser Thr Gly Ile Leu Ser Val Ile Gly Val Met Leu -10 -15 Ala Pro Phe Thr Ala Gly Leu Ser Leu Ser Ile Thr Ala Ala Gly Val 1 Gly Leu Gly Ile Ala Ser Ala Thr Ala Gly Ile Ala Ser Ser Ile Val 15 20 Glu Asn Thr Tyr Thr Arg Ser Ala Glu Leu Thr Ala Ser Arg Leu Thr 35 Ala Thr Ser Thr Asp Gln Leu Glu Ala Leu Arg Asp Ile Leu His Asp 50 Ile Thr Pro Asn Val Leu Ser Phe Ala Leu Asp Phe Asp Glu Ala Thr WO 99/31236 -117- PCT/IB98/02122 .

```
65
Lys Met Ile Ala Asn Asp Val His Thr Leu Arg Arg Ser Lys Ala Thr
75 80
                  85 90
Val Gly Arg Pro Leu Ile Ala Trp Arg Tyr Val Pro Ile Asn Val Val
               100 105
          95
Glu Thr Leu Arg Thr Arg Gly Ala Pro Thr Arg Ile Val Arg Lys Val
      110 115 120
Ala Arg Asn Leu Gly Lys Ala Thr Ser Gly Val Leu Val Val Leu Asp
     125 130
Val Val Asn Leu Val Gln Asp Ser Leu Asp Leu His Lys Gly Glu Lys
                 145
Ser Glu Ser Ala Glu Leu Leu Arg Gln Trp Ala Gln Glu Leu Glu Glu
155 160
                            165 170
Asn Leu Asn Glu Leu Thr His Ile His Gln Ser Leu Lys Ala Gly
           175
                          180
```

Cys Gly Ser His Leu Trp Arg Glu Ser His His

5 ·

<210> 148 <211> 180 <212> PRT <213> Homo sapiens

<400> 148

<210> 147

Met Cys Ile Ser Gly Leu Cys Gln Ile Val Gly Cys Asp His Gln Leu Gly Ser Thr Val Lys Glu Asp Asn Cys Gly Val Cys Asn Gly Asp Gly 25 20 Ser Thr Cys Arg Leu Val Arg Gly Gln Tyr Lys Ser Gln Leu Ser Ala 40 45 Thr Lys Ser Asp Asp Thr Val Val Ala Ile Pro Tyr Gly Ser Arg His 55 60 Ile Arg Leu Val Leu Lys Gly Pro Asp His Leu Tyr Leu Glu Thr Lys 70 75 Thr Leu Gln Gly Thr Lys Gly Glu Asn Ser Leu Ser Ser Thr Gly Thr 90 85 Phe Leu Val Asp Asn Ser Ser Val Asp Phe Gln Lys Phe Pro Asp Lys 100 105 Glu Ile Leu Arg Met Ala Gly Pro Leu Thr Ala Asp Phe Ile Val Lys 120 125 Ile Arg Asn Ser Gly Ser Ala Asp Ser Thr Val Gln Phe Ile Phe Tyr

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```
140
  130
                   135
Gln Pro Ile Ile His Arg Trp Arg Glu Thr Asp Phe Phe Pro Cys Ser
145 150 155 160
Ala Thr Cys Gly Gly Gly Tyr Gln Leu Thr Ser Ala Glu Cys Tyr Asp
                    170
Leu Arg Ser Asn
        180
<210> 149
<211> 162
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 149
Met Gly Asp Lys Ile Trp Leu Pro Phe Pro Val Leu Leu Leu Ala Ala
        -20 -15
Leu Pro Pro Val Leu Leu Pro Gly Ala Ala Gly Phe Thr Pro Ser Leu
                      1
Asp Ser Asp Phe Thr Phe Thr Leu Pro Ala Gly Gln Lys Glu Cys Phe
10 15
Tyr Gln Pro Met Pro Leu Lys Ala Ser Leu Glu Ile Glu Tyr Gln Val
            30
                              35
Leu Asp Gly Ala Gly Leu Asp Ile Asp Phe His Leu Ala Ser Pro Glu
                           50
Gly Lys Thr Leu Val Phe Glu Gln Arg Lys Ser Asp Gly Val His Thr
Val Glu Thr Glu Val Gly Asp Tyr Met Phe Cys Phe Asp Asn Thr Phe
                                    85
Ser Thr Ile Ser Glu Lys Val Ile Phe Phe Glu Leu Ile Pro Asp Asn
                               100 105
                95
Met Gly Glu Gln Ala Gln Glu Gln Glu Asp Trp Lys Lys Tyr Ile Thr
            110 115 120
Gly Thr Asp Ile Leu Asp Met Lys Leu Glu Asp Ile Leu Val Ser Met
                   130
Val Phe
<210> 150
<211> 120
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 150
Met Gly Asp Lys Ile Trp Leu Pro Phe Pro Val Leu Leu Leu Ala Ala
         -20 -15 -10
```

Leu Pro Pro Val Leu Leu Pro Gly Ala Ala Gly Phe Thr Pro Ser Leu

Asp Ser Asp Phe Thr Phe Thr Leu Pro Ala Gly Gln Lys Glu Cys Phe

Tyr Gln Pro Met Pro Leu Lys Ala Ser Leu Glu Ile Glu Tyr Gln Val

20

35

1

-5

15

<210> 151 <211> 7 <212> PRT <213> Homo sapiens <400> 151 Met Val Glu Met Thr Gly Val 1 5

<210> 152 <211> 199 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -42..-1

<400> 152

Met Asp Gly Gln Lys Lys Asn Trp Lys Asp Lys Val Val Asp Leu Leu -35 Tyr Trp Arg Asp Ile Lys Lys Thr Gly Val Val Phe Gly Ala Ser Leu -20 -15 Phe Leu Leu Ser Leu Thr Val Phe Ser Ile Val Ser Val Thr Ala 1 - 5 Tyr Ile Ala Leu Ala Leu Leu Ser Val Thr Ile Ser Phe Arg Ile Tyr 15 10 Lys Gly Val Ile Gln Ala Ile Gln Lys Ser Asp Glu Gly His Pro Phe 30 Arg Ala Tyr Leu Glu Ser Glu Val Ala Ile Ser Glu Glu Leu Val Gln 45 Lys Tyr Ser Asn Ser Ala Leu Gly His Val Asn Cys Thr Ile Lys Glu 60 Leu Arg Arg Leu Phe Leu Val Asp Asp Leu Val Asp Ser Leu Lys Phe 80 Ala Val Leu Met Trp Val Phe Thr Tyr Val Gly Ala Leu Phe Asn Gly 95 90 Leu Thr Leu Leu Ile Leu Ala Leu Ile Ser Leu Phe Ser Val Pro Val 110 Ile Tyr Glu Arg His Gln Ala Gln Ile Asp His Tyr Leu Val Leu Ala 125 130 Asn Lys Asn Val Lys Asp Ala Met Ala Lys Ile Gln Ala Lys Ile Pro 140 145 Gly Leu Lys Arg Lys Ala Glu

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```
<211> 43
<212> PRT
<213> Homo sapiens
<400> 153
Met Pro Phe Arg Met Ser Gly Tyr Ile Pro Phe Gly Thr Pro Ile Val
1 5
                         10
Ser Val Thr Phe Lys Gly Phe Pro Phe Leu Lys Asn Tyr Phe Lys Cys
                25
Leu Thr Leu Cys Tyr Cys Ser Arg Val Phe Asp
<210> 154
<211> 50
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 154
Met Glu Trp Ala Gly Lys Gln Arg Asp Phe Gln Val Arg Ala Ala Pro
    -35 -30
                                     -25
Gly Trp Asp His Leu Ala Ser Phe Pro Gly Pro Ser Leu Arg Leu Phe
-20 -15 -10
Ser Gly Ser Gln Ala Ser Val Cys Ser Leu Cys Ser Gly Phe Gly Ala
                      5
~5 . 1
Gln Glu
<210> 155
<211> 153
<212> PRT
<213> Homo sapiens
<400> 155
Thr Val Pro Leu Leu Glu Pro Ala Asp His Ala Arg Gly Arg Ala
                           10
1 5
His Val His Leu Pro Glu Asn Val Arg Ser Gln Ser Pro Gly His Val
   20
                        25
Arg Arg Gly Arg Ser Gly Ala Gln Val Leu Pro Thr Gly Pro Asp Glu
                     40
                                    45
Lys Gln Val Glu Lys Ser Glu Val Asp Phe Ser Lys Ser His Ser Leu
                  55
                      60
Val Arg Arg Phe Glu Asp Leu Lys Pro Lys Leu Ser Val Cys Lys Thr
                              75
              70
Gly Ser Gln Val Phe Arg Ser Glu Asn Trp Lys Val Trp Ala Glu Ser
                           90
           85
Ser Arg Gly Asp His Asp Asp Cys Leu Asp Leu Cys Ser Val Leu Cys
                        105
        100
Trp Gly Glu Leu Leu Arg Thr Ile Pro Glu Ile Pro Pro Lys Arg Gly
     115 120
                                    125
Glu Leu Lys Thr Glu Leu Leu Gly Leu Lys Glu Arg Lys His Lys Pro
  130 135
```

Gln Val Ser Gln Gln Glu Glu Leu Lys

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```
<210> 156
<211> 67
<212> PRT
<213> Homo sapiens
<400> 156
Met Arg Gln Lys Arg Lys Gly Asp Leu Ser Pro Ala Lys Leu Met Met
                               10
Leu Thr Ile Gly Asp Val Ile Lys Gln Leu Ile Glu Ala His Glu Gln
          20
                   25
Gly Lys Asp Ile Asp Leu Asn Lys Val Arg Thr Lys Thr Ala Ala Lys
                 40
Tyr Gly Leu Ser Ala Gln Pro Arg Leu Val Asp Ile Ile Ala Ala Val
              55
  50
Pro Pro Glu
65
<210> 157
<211> 87
<212> PRT
<213> Homo sapiens
<400> 157
Met Asp Glu Leu Ser Glu Glu Asp Lys Leu Thr Val Ser Arg Ala Arg
       5
                               10
Lys Ile Gln Arg Phe Leu Ser Gln Pro Phe Gln Val Ala Glu Val Phe
         20
                          25
Thr Gly His Met Gly Lys Leu Val Pro Leu Lys Glu Thr Ile Lys Gly
                      40
Phe Gln Gln Ile Leu Ala Gly Glu Tyr Asp His Leu Pro Glu Gln Ala
 50 - 55
                             60
Phe Tyr Met Val Gly Pro Ile Glu Glu Ala Val Ala Lys Ala Asp Lys
                             75
           70
Leu Ala Glu Glu His Ser Ser
              85
<210> 158
<211> 250
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -85..-1
Met Ser Ala Glu Val Lys Val Thr Gly Gln Asn Gln Glu Gln Phe Leu
-85 -80
                      -75
Leu Leu Ala Lys Ser Ala Lys Gly Ala Ala Leu Ala Thr Leu Ile His
              -65
                               -60
Gln Val Leu Glu Ala Pro Gly Val Tyr Val Phe Gly Glu Leu Leu Asp
                            -45
        -50
Met Pro Asn Val Arg Glu Leu Xaa Ala Arg Asn Leu Pro Pro Leu Thr
      -35
                        -30
                                -25
```

Glu Ala Gln Lys Asn Lys Leu Arg His Leu Ser Val Val Thr Leu Ala

Ala Lys Val Lys Cys Ile Pro Tyr Ala Val Leu Leu Glu Ala Leu Ala

-10

-15

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```
Leu Arg Asn Val Arg Gln Leu Glu Asp Leu Val Ile Glu Ala Val Tyr
                20
Ala Asp Val Leu Arg Gly Ser Leu Asp Gln Arg Asn Gln Arg Leu Glu
Val Asp Tyr Ser Ile Gly Arg Asp Ile Gln Arg Gln Asp Leu Ser Ala
Ile Ala Arg Thr Leu Gln Glu Trp Cys Val Gly Cys Glu Val Val Leu
                 65
                                    70
Ser Gly Ile Glu Glu Gln Val Ser Arg Ala Asn Gln His Lys Glu Gln
                                85
Gln Leu Gly Leu Lys Gln Gln Ile Glu Ser Glu Val Ala Asn Leu Lys
                              100
Lys Thr Ile Lys Val Thr Thr Ala Ala Ala Ala Ala Thr Ser Gln
                        115
Asp Pro Glu Gln His Leu Thr Glu Leu Arg Glu Pro Ala Pro Gly Thr
                     130
Asn Gln Arg Gln Pro Ser Lys Lys Ala Ser Lys Gly Lys Gly Leu Arg
                  145
Gly Ser Ala Lys Ile Trp Ser Lys Ser Asn
```

<210> 159 <211> 24 <212> PRT <213> Homo sapiens

<400> 159

Met Pro Thr Asn Cys Ala Ala Ala Gly Cys Ala Thr Thr Tyr Asn Lys

1 5 10 15

His Ile Asn Ile Ser Phe His Arg
20

<210> 160 <211> 228 <212> PRT <213> Homo sapiens

<400> 160

Met Pro Thr Asn Cys Ala Ala Ala Gly Cys Ala Thr Thr Tyr Asn Lys 10 His Ile Asn Ile Ser Phe His Arg Phe Pro Leu Asp Pro Lys Arg Arg 25 Lys Glu Trp Val Arg Leu Val Arg Arg Lys Asn Phe Val Pro Gly Lys 40 His Thr Phe Leu Cys Ser Lys His Phe Glu Ala Ser Cys Phe Asp Leu 55 Thr Gly Gln Thr Arg Arg Leu Lys Met Asp Ala Val Pro Thr Ile Phe 75 70 Asp Phe Cys Thr His Ile Lys Ser Met Lys Leu Lys Ser Arg Asn Leu 90 Leu Lys Lys Asn Asn Ser Cys Ser Pro Ala Gly Pro Ser Ser Leu Lys 105 Ser Asn Ile Ser Ser Gln Gln Val Leu Leu Glu His Ser Tyr Ala Phe 120 Arg Asn Pro Met Glu Ala Lys Lys Arg Ile Ile Lys Leu Glu Lys Glu 130 135 140 Ile Ala Ser Leu Arg Arg Lys Met Lys Thr Cys Leu Gln Lys Glu Arg WO 99/31236 -123- PCT/IB98/02122

```
155
               150
Arg Ala Thr Arg Arg Trp Ile Lys Ala Met Cys Leu Val Lys Asn Leu
       165 170 175
Glu Ala Asn Ser Val Leu Pro Lys Gly Thr Ser Glu His Met Leu Pro
        180 185 190
Thr Ala Leu Ser Ser Leu Pro Leu Glu Asp Phe Lys Ile Leu Glu Gln
      195 200 205
Asp Gln Gln Asp Lys Thr Leu Leu Ser Leu Asn Leu Lys Gln Thr Lys
                215
Ser Thr Phe Ile
225
<210> 161
<211> 86
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -20..-1
<400> 161
Met Asn Leu His Phe Pro Gln Trp Phe Val His Ser Ser Ala Leu Gly
-20 -15 -10 -5
Leu Val Leu Ala Pro Pro Phe Ser Ser Pro Gly Thr Asp Pro Thr Phe
          1 5
Pro Cys Ile Tyr Cys Arg Leu Leu Asn Met Ile Met Thr Arg Leu Ala
                   20
Phe Ser Phe Ile Thr Cys Leu Cys Pro Asn Leu Lys Glu Val Cys Leu
                 35
                         40
Ile Leu Pro Glu Lys Asn Cys Asn Ser Arg His Ala Gly Phe Val Gly
                              55
             50
Pro Ala Lys Leu Arg Gln
            65
<210> 162
<211> 44
<212> PRT
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<210> 163 <211> 314 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -58..-1

<400> 163 Met Gln Asn Val Ile Asn Thr Val Lys Gly Lys Ala Leu Glu Val Ala -50 -45 -55 Glu Tyr Leu Thr Pro Val Leu Lys Glu Ser Lys Phe Arg Glu Thr Gly -30 -35 Val Ile Thr Pro Glu Glu Phe Val Ala Ala Gly Asp His Leu Val His -15 -20 His Cys Pro Thr Trp Gln Trp Ala Thr Gly Glu Glu Leu Lys Val Lys -10 -5 1 5 Ala Tyr Leu Pro Thr Gly Lys Gln Phe Leu Val Thr Lys Asn Val Pro 10 15 Cys Tyr Lys Arg Cys Lys Gln Met Glu Tyr Ser Asp Glu Leu Glu Ala 25 30 35 Ile Ile Glu Glu Asp Asp Gly Asp Gly Gly Trp Val Asp Thr Tyr His 45 Asn Thr Gly Ile Thr Gly Ile Thr Glu Ala Val Lys Glu Ile Thr Leu 65 60 Glu Asn Lys Asp Asn Ile Arg Leu Gln Asp Cys Ser Ala Leu Cys Glu 75 80 Glu Glu Glu Asp Glu Asp Glu Gly Glu Ala Ala Asp Met Glu Glu Tyr 95 Glu Glu Ser Gly Leu Leu Glu Thr Asp Glu Ala Thr Leu Asp Thr Arg 110 Lys Ile Val Glu Ala Cys Lys Ala Lys Thr Asp Ala Gly Gly Glu Asp 125 130 Ala Ile Leu Gln Thr Arg Thr Tyr Asp Leu Tyr Ile Thr Tyr Asp Lys 140 145 Tyr Tyr Gln Thr Pro Arg Leu Trp Leu Phe Gly Tyr Asp Glu Gln Arg 160 Gln Pro Leu Thr Val Glu His Met Tyr Glu Asp Ile Ser Gln Asp His 175 Val Lys Lys Thr Val Thr Ile Glu Asn His Pro His Leu Pro Pro Pro 190 Pro Met Cys Ser Val His Pro Cys Arg His Ala Glu Val Met Lys Lys 205 210 Ile Ile Glu Thr Val Ala Glu Gly Gly Glu Leu Gly Val His Met 220 225 Tyr Leu Leu Ile Phe Leu Lys Phe Val Gln Ala Val Ile Pro Thr Ile 235 240 Glu Tyr Asp Tyr Thr Arg His Phe Thr Met 250

<210> 164 <211> 89 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<400> 164

<222> -80..-1

```
-25
Gln Leu Gly Arg Gly Leu Leu Ser Ala Cys Ala Pro Trp Gly Asp Gly
 -15 -10 -5
Ser Thr Gln Pro Val Pro Leu Cys Ser
1 5
<210> 165
<211> 98
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -15..-1
<400> 165
Met Glu Ala Met Trp Leu Leu Cys Val Ala Leu Ala Val Leu Ala Trp
                 -10
                                    -5
Gly Phe Leu Trp Val Trp Asp Ser Ser Glu Arg Met Lys Ser Arg Glu
                            10
Gln Gly Gly Arg Leu Gly Ala Glu Ser Arg Thr Leu Leu Val Ile Ala
                         25
His Pro Asp Asp Glu Ala Met Phe Phe Ala Pro Thr Val Leu Gly Leu
                     40
                                       45
Ala Arg Leu Arg His Trp Val Tyr Leu Leu Cys Phe Ser Ala Val Phe
                 55
                                  60
Arg Arg Glu Leu Ser Glu Tyr Thr Glu Gly Leu Thr Ser Glu Pro Leu
Thr Ala
<210> 166
<211> 92
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -36..-1
<400> 166
Met Leu Val Thr Gln Gly Leu Val Tyr Gln Gly Tyr Leu Ala Ala Asn
                                       -25
                    -30
Ser Arg Phe Gly Ser Leu Pro Lys Val Ala Leu Ala Gly Leu Leu Gly
```

<210> 167 <211> 351 <212> PRT WO 99/31236 -126- PCT/IB98/02122 -

<213> Homo sapiens <220> <221> SIGNAL <222> -16..-1 <400> 167 Met Val Pro Phe Ile Tyr Leu Gln Ala His Phe Thr Leu Cys Ser Gly -10 Trp Ser Ser Thr Tyr Arg Asp Leu Arg Lys Gly Val Tyr Val Pro Tyr 10 Thr Gln Gly Lys Trp Glu Gly Glu Leu Gly Thr Asp Leu Val Ser Ile 25 Pro His Gly Pro Asn Val Thr Val Arg Ala Asn Ile Ala Ala Ile Thr 40 Glu Ser Asp Lys Phe Phe Ile Asn Gly Ser Asn Trp Glu Gly Ile Leu 60 Gly Leu Ala Tyr Ala Glu Ile Ala Arg Pro Asp Asp Ser Pro Glu Pro 70 75 Phe Phe Asp Ser Leu Val Lys Gln Thr His Val Pro Asn Leu Phe Ser 90 85 Leu Gln Leu Cys Gly Ala Gly Phe Pro Leu Asn Gln Ser Glu Val Leu 105 Ala Ser Val Gly Gly Ser Met Ile Ile Gly Gly Ile Asp His Ser Leu 115 120 125 Tyr Thr Gly Ser Leu Trp Tyr Thr Pro Ile Arg Arg Glu Trp Tyr Tyr 140 135 Glu Val Ile Ile Val Arg Val Glu Ile Asn Gly Gln Asp Leu Lys Met 150 155 Asp Cys Lys Glu Tyr Asn Tyr Asp Lys Ser Ile Val Asp Ser Gly Thr 170 165 Thr Asn Leu Arg Leu Pro Lys Lys Val Phe Glu Ala Ala Val Lys Ser 180 185 190 Ile Lys Ala Ala Ser Ser Thr Glu Lys Phe Pro Asp Gly Phe Trp Leu 195 200 205 Gly Glu Gln Leu Val Cys Trp Gln Ala Gly Thr Thr Pro Trp Asn Ile 215 220 Phe Pro Val Ile Ser Leu Tyr Leu Met Gly Glu Val Thr Asn Gln Ser 230 235 Phe Arg Ile Thr Ile Leu Pro Gln Gln Tyr Leu Arg Pro Val Glu Asp 245 250 Val Ala Thr Ser Gln Asp Asp Cys Tyr Lys Phe Ala Ile Ser Gln Ser 265 270 260 Ser Thr Gly Thr Val Met Gly Ala Val Ile Met Glu Gly Phe Tyr Val 280 285 Val Phe Asp Arg Ala Arg Lys Arg Ile Gly Phe Ala Val Ser Ala Cys 295 300 His Val His Asp Glu Phe Arg Thr Ala Ala Val Glu Gly Pro Phe Cys

<210> 168 <211> 138 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<222> -47..-1

305 310 315

325

His Leu Gly His Gly Arg Leu Trp Leu Gln His Ser Thr Asp Arg

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```
<400> 168
Met Glu Lys Phe Val Asp Pro Gly Asn His Asn Ser Gly Ile Asp Leu
    -45 -40 -35
Leu Arg Thr Tyr Leu Trp Arg Cys Gln Phe Leu Leu Pro Phe Val Ser
                         -20
          -25
Leu Gly Leu Met Cys Phe Gly Ala Leu Ile Gly Leu Cys Ala Cys Ile
                      -5.
-15 -10
Cys Arg Ser Leu Tyr Pro Thr Ile Ala Thr Gly Ile Leu His Leu Leu
   5 10 15
Ala Gly Leu Cys Thr Leu Gly Ser Val Ser Cys Tyr Val Ala Gly Ile
            25 30
Glu Leu Leu His Gln Lys Leu Glu Leu Pro Asp Asn Val Ser Gly Glu
                        45
               40
Phe Gly Trp Ser Phe Cys Leu Ala Cys Val Ser Ala Pro Leu Gln Phe
             55 60 65
Met Ala Ser Ala Leu Phe Ile Trp Ala Ala His Thr Asn Arg Arg Glu
         70
                 75
Tyr Thr Leu Met Lys Ala Tyr Arg Val Ala
         85
<210> 169
<211> 101
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -73..-1
<400> 169
Met Asn Leu Glu Arg Val Ser Asn Glu Glu Lys Leu Asn Leu Cys Arg
   <del>-</del>70 -65 -60
Lys Tyr Tyr Leu Gly Gly Phe Ala Phe Leu Pro Phe Leu Trp Leu Val
Asn Ile Phe Trp Phe Tyr Arg Glu Ala Phe Leu Val Pro Ala Tyr Thr
                -35 -30
Glu Gln Ser Gln Ile Lys Gly Tyr Val Trp Arg Ser Ala Val Gly Phe
                       -15 -10
               -20
Leu Phe Trp Val Ile Val Leu Thr Ser Trp Ile Thr Ile Phe Gln Ile
                   1
Tyr Arg Pro Arg Trp Gly Ala Leu Gly Asp Tyr Leu Ser Phe Thr Ile
    10
Pro Leu Gly Thr Pro
   25
<210> 170
<211> 252
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -68..-1
```

Met Pro Glu Gly Pro Glu Leu His Leu Ala Ser Gln Phe Val Asn Glu

-60

-65

-55

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```
Ala Cys Arg Ala Leu Val Phe Gly Gly Cys Val Glu Lys Ser Ser Val
                       -45
Ser Arg Asn Pro Glu Val Pro Phe Glu Ser Ser Ala Tyr Arg Ile Ser
                      -30
Ala Ser Ala Arg Gly Lys Glu Leu Arg Leu Ile Leu Ser Pro Leu Pro
                 -15
                                   -10
Gly Ala Gln Pro Gln Gln Glu Pro Leu Ala Leu Val Phe Arg Phe Gly
            1
Met Ser Gly Ser Phe Gln Leu Val Pro Arg Glu Glu Leu Pro Arg His
                          20
Ala His Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu
                      35
Cys Phe Val Asp Ile Arg Arg Phe Gly Arg Trp Asp Leu Gly Gly Lys
                                    55
Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Phe
                                  70
Arg Glu Asn Val Leu Arg Asn Leu Ala Asp Lys Ala Phe Asp Arg Pro
                             85
Ile Cys Glu Ala Leu Leu Asp Gln Arg Phe Phe Asn Gly Ile Gly Asn
                         100
                                  105
Tyr Leu Arg Ala Glu Ile Leu Tyr Arg Leu Lys Ile Pro Pro Phe Glu
                                        120
                      115
Lys Ala Arg Ser Val Leu Glu Ala Leu Gln Gln His Arg Pro Ser Pro
                  130
                                     135
Glu Leu Thr Leu Ser Gln Lys Ile Arg Thr Lys Leu Gln Asn Ser Asp
                                 150
Leu Leu Glu Leu Cys His Ser Val Pro Lys Glu Val Val Gln Leu Gly
                             165
Glu Ala Lys Asp Gly Ser Asn Leu Cys Phe Ser Lys
                         180
```

```
<210> 171
<211> 350
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -68..-1
<400> 171
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Met Pro Glu Gly Pro Glu Leu His Leu Ala Ser Gln Phe Val Asn Glu -60 -65 Ala Cys Arg Ala Leu Val Phe Gly Gly Cys Val Glu Lys Ser Ser Val -45 -40 -50 Ser Arg Asn Pro Glu Val Pro Phe Glu Ser Ser Ala Tyr Arg Ile Ser -25 ~30 Ala Ser Ala Arg Gly Lys Glu Leu Arg Leu Ile Leu Ser Pro Leu Pro -15 -10 Gly Ala Gln Pro Gln Gln Glu Pro Leu Ala Leu Val Phe Arg Phe Gly Met Ser Gly Ser Phe Gln Leu Val Pro Arg Glu Glu Leu Pro Arg His 20 Ala His Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu 35 40 Cys Phe Val Asp Ile Arg Arg Phe Gly Arg Trp Asp Leu Gly Gly Lys 5.5 50 Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Glr. Glu Tyr Gln Gln Phe 70 Arg Leu Lys Ile Pro Pro Phe Glu Lys Ala Arg Ser Val Leu Glu Ala

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```
85
        80
Leu Gln Gln His Arg Pro Ser Pro Glu Leu Thr Leu Ser Gln Lys Ile
  95 100 105
Arg Thr Lys Leu Gln Asn Pro Asp Leu Leu Glu Leu Cys His Ser Val
                         120
         115
Pro Lys Glu Val Asp Gln Leu Gly Gly Arg Gly Tyr Gly Ser Glu Ser
                              135 140
        130
Gly Glu Glu Asp Phe Ala Ala Phe Arg Ala Trp Leu Arg Cys Tyr Gly
                           150 155
           145
Met Pro Gly Met Ser Ser Leu Gln Asp Arg His Gly Arg Thr Ile Trp
        160
                        165
Phe Gln Gly Asp Pro Gly Pro Leu Ala Pro Lys Gly Arg Lys Ser Arg
     175
                    180
                                    185
Lys Lys Lys Ser Lys Ala Thr Gln Leu Ser Pro Glu Asp Arg Val Glu
                  195 200
Asp Ala Leu Pro Pro Ser Lys Ala Pro Ser Lys Thr Arg Arg Ala Lys
   210
                              215
Arg Asp Leu Pro Lys Arg Thr Ala Thr Gln Arg Pro Glu Gly Thr Ser
                           230
            225
Leu Gln Gln Asp Pro Glu Ala Pro Thr Val Pro Lys Lys Gly Arg Arg
        240 245
Lys Gly Arg Gln Ala Ala Ser Gly His Cys Arg Pro Arg Lys Val Lys
                     260 265
Ala Asp Ile Pro Ser Leu Glu Pro Glu Gly Thr Ser Ala Ser
                 275
```

-60 -65 Ala Cys Arg Ala Leu Val Phe Gly Gly Cys Val Glu Lys Ser Ser Val -45 Ser Arg Asn Pro Glu Val Pro Phe Glu Ser Ser Ala Tyr Arg Ile Ser -30 -25 Ala Ser Ala Arg Gly Lys Glu Leu Arg Leu Ile Leu Ser Pro Leu Pro -15 -10 Gly Ala Gln Pro Gln Gln Glu Pro Leu Ala Leu Val Phe Arg Phe Gly 1 5 Met Ser Gly Ser Phe Gln Leu Val Pro Arg Glu Glu Leu Pro Arg His 20 Ala His Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu 35 Cys Phe Val Asp Ile Arg Arg Phe Gly Arg Trp Asp Leu Gly Gly Lys 55 50 Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Phe 70 65 Arg Glu Asn Val Leu Arg Asn Leu Ala Asp Lys Ala Phe Asp Arg Pro 85 . 80 Ile Cys Glu Ala Leu Leu Asp Gln Arg Phe Phe Asn Gly Ile Gly Asn 105 100 Tyr Leu Arg Ala Glu Ile Leu Tyr Arg Leu Lys Ile Pro Pro Phe Glu 120 115 110

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Lys Ala Arg Ser Val Leu Glu Ala Leu Gln Gln His Arg Pro Ser Pro 130 135 Glu Leu Thr Leu Ser Gln Lys Ile Arg Thr Lys Leu Gln Asn Pro Asp 150 Leu Leu Glu Leu Cys His Ser Val Pro Lys Glu Val Val Gln Leu Gly 165 Gly Arg Gly Tyr Gly Ser Glu Ser Gly Glu Glu Asp Phe Ala Ala Phe 180 185 Arg Ala Trp Leu Arg Cys Tyr Gly Met Pro Gly Met Ser Ser Leu Gln 200 195 Asp Arg His Gly Arg Thr Ile Trp Phe Gln Gly Asp Pro Gly Pro Leu 210 215 Ala Pro Lys Gly Arg Lys Ser Arg Lys Lys Lys Ser Lys Ala Thr Gln 225 230 Leu Ser Pro Glu Asp Arg Val Glu Asp Ala Leu Pro Pro Ser Lys Ala 245 240 Pro Ser Arg Thr Arg Arg Ala Lys Arg Asp Leu Pro Lys Arg Thr Ala 265 260 Thr Gln Arg Pro Glu Gly Thr Ser Leu Gln Gln Asp Pro Glu Ala Pro 280 275 Thr Val Pro Lys Lys Gly Arg Lys Gly Arg Gln Ala Ala Ser Gly 295 290 His Cys Arg Pro Arg Lys Val Lys Ala Asp Ile Pro Ser Leu Glu Pro 310 305 Glu Gly Thr Ser Ala Ser 320

<212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -82..-1 <400> 173 Met Tyr Val Trp Pro Cys Ala Val Val Leu Ala Gln Tyr Leu Trp Phe -75 -80 His Arg Arg Ser Leu Pro Gly Lys Ala Ile Leu Glu Ile Gly Ala Gly -60 Val Ser Leu Pro Gly Ile Leu Thr Ala Lys Cys Gly Ala Glu Val Ile -45 -40 Leu Ser Asp Ser Ser Glu Leu Pro His Cys Leu Glu Val Cys Arg Gln -25 -30 Ser Cys Gln Met Asn Asn Leu Pro His Leu Gln Val Val Gly Leu Thr -15 -10 -5 Trp Gly His Ile Ser Trp Asp Leu Leu Ala Leu Pro Pro Gln Asp Ile 10 Ile Leu Ala Ser Asp Val Phe Phe Glu Pro Glu Asp Phe Glu Asp Ile 20 Leu Ala Thr Ile Tyr Phe Leu Met His Lys Asn Pro Lys Val Gln Leu Trp Ser Thr Tyr Gln Val Arg Ser Ala Asp Trp Ser Leu Glu Ala Leu 55 Leu Tyr Lys Trp Asp Met Lys Cys Val His Ile Pro Leu Glu Ser Phe Asp Ala Asp Lys Glu Asp Ile Ala Glu Ser Thr Leu Pro Gly Arg His 85 Thr Val Glu Met Leu Val Ile Ser Phe Ala Lys Asp Ser Leu

<210> 173 <211> 190

<210> 174

95 100 105

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<211> 285
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -232..-1
<400> 174
Met Gly Cys Val Phe Gln Ser Thr Glu Asp Lys Arg Ile Phe Lys Ile
    -230 -225
Asp Trp Thr Leu Ser Pro Gly Glu His Ala Lys Asp Glu Tyr Val Leu
-215 -210 -205
Tyr Tyr Tyr Ser Asn Leu Ser Val Pro Ile Gly Arg Phe Gln Asn Arg
-200 -195 -190 -185
Val His Leu Met Gly Asp Asn Leu Cys Asn Asp Gly Ser Leu Leu Leu
          -180 -175 -170
Gln Asp Val Gln Glu Ala Asp Gln Gly Thr Tyr Ile Cys Glu Ile Arg
        -165 -160 -155
Leu Lys Gly Glu Ser Gln Val Phe Lys Lys Ala Val Val Leu His Val
     -150 -145 -140
Leu Pro Glu Glu Pro Lys Glu Leu Met Val His Val Gly Gly Leu Ile
  -135 -130
                               -125
Gln Met Gly Cys Val Phe Gln Ser Thr Glu Val Lys His Val Thr Lys
                           -110 -105
     -115
Val Glu Trp Ile Phe Ser Gly Arg Arg Ala Lys Glu Glu Ile Val Phe
                         -95 -90
           -100
Arg Tyr Tyr His Lys Leu Arg Met Ser Ala Glu Tyr Ser Gln Ser Trp
        -85 -80 -75
Gly His Phe Gln Asn Arg Val Asn Leu Val Gly Asp Ile Phe Arg Asn
                   -65
Asp Gly Ser Ile Met Leu Gln Gly Val Arg Glu Ser Asp Gly Gly Asn
  -55 -50
                               -45
Tyr Thr Cys Ser Ile His Leu Gly Asn Leu Val Phe Lys Lys Thr Ile
     -35 -30 -25
-40
Val Leu His Val Ser Pro Glu Glu Pro Arg Thr Leu Val Thr Pro Ala
         -20 -15 -10
Ala Leu Arg Pro Leu Val Leu Gly Gly Asn Gln Leu Val Ile Ile Val
        -5 1 5
Gly Ile Val Cys Ala Thr Ile Leu Leu Pro Val Leu Ile Leu Ile
  10 15 20
Val Lys Lys Thr Cys Gly Asn Lys Ser Ser Val Asn Ser Thr Val Leu
25 30 35
Val Lys Asn Thr Lys Lys Thr Asn Pro Lys Lys Lys
           45
                 50
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<210> 175 <211> 153

<212> PRT

<213> Homo sapiens

<400> 175

Met Gly Cys Val Phe Gln Ser Thr Val Asp Lys Cys Ile Phe Lys Ile 1 5 10 15 Asp Trp Thr Leu Ser Pro Gly Glu His Ala Lys Asp Glu Tyr Val Leu

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25 Tyr Tyr Tyr Ser Asn Leu Ser Val Pro Ile Gly Arg Phe Gln Asn Arg 35 40 Val His Leu Met Gly Asp Ile Leu Cys Asn Asp Gly Ser Leu Leu 55 Gln Asp Val Gln Glu Ala Asp Gln Gly Thr Tyr Ile Cys Glu Ile Arg 75 70 Leu Lys Gly Glu Ser Gln Val Phe Lys Lys Ala Val Val Leu His Val 90 Leu Pro Glu Glu Pro Lys Glu Leu Met Val His Val Gly Gly Leu Ile 105 100 Gln Met Gly Cys Val Phe Gln Ser Thr Glu Val Lys His Val Thr Lys 120 Val Glu Trp Ile Phe Ser Gly Arg Arg Ala Lys Val Thr Arg Arg Lys 135 His His Cys Val Arg Glu Gly Ser Gly 150

<210> 176 <211> 49 <212> PRT <213> Homo sapiens

Cys

<210> 177 <211> 99 <212> PRT <213> Homo sapiens

<220>
<221> SIGNAL
<222> -24..-1

<400> 177 Met Lys Ser Ala Lys Leu Gly Phe Leu Leu Arg Phe Phe Ile Phe Cys -15 -20 Ser Leu Asn Thr Leu Leu Gly Gly Val Asn Lys Ile Ala Glu Lys - 5 1 Ile Cys Gly Asp Leu Lys Asp Pro Cys Lys Leu Asp Met Asn Phe Gly 20 15 Ser Cys Tyr Glu Val His Phe Arg Tyr Phe Tyr Asn Arg Thr Ser Lys 35 30 Arg Cys Glu Thr Phe Val Phe Ser Gly Cys Asn Gly Asn Leu Asn Asn 45 50 Phe Lys Leu Lys Ile Glu Arg Glu Val Ala Cys Val Ala Lys Tyr Lys 65 Pro Pro Arg 75

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<210> 178
<211> 95
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 178
Met Ala Ser Pro Ala Val Asn Arq Trp Lys Arq Pro Arq Leu Lys Pro
 -35
                       -30
                              -25
Val Trp Pro Arg Arg Leu Glu Ser Trp Leu Leu Leu Asp Ala Leu Leu
 -20
                           -10
                   -15
Arg Leu Gly Asp Thr Lys Lys Lys Arg Gln Pro Glu Ala Ala Thr Lys
-5
             1 5
Ser Cys Val Arg Ser Ser Cys Gly Gly Pro Ser Gly Asp Gly Pro Pro
                               25
      15
             20
Pro Cys Leu Gln Gln Pro Asp Pro Arg Ala Leu Ser Gln Ala Phe Ser
 30 35
Arg Ser Phe Pro Leu Phe Pro Ser Leu Ala Gly Lys Ser Met Ile
  45 50
                                   5.5
<210> 179
<211> 121
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 179
Met Met Leu Pro Gln Trp Leu Leu Leu Phe Leu Leu Phe Phe Phe
        -20 -15
                                        -10
Leu Phe Leu Leu Thr Arg Gly Ser Leu Ser Pro Thr Lys Tyr Asn Leu
                     1
Leu Glu Leu Lys Glu Ser Cys Ile Arg Asn Gln Asp Cys Glu Thr Gly
               15
                                20
Cys Cys Gln Arg Ala Pro Asp Asn Cys Glu Ser His Cys Ala Glu Lys
            30
                             35
Gly Ser Glu Gly Ser Leu Cys Gln Thr Gln Val Phe Phe Gly Gln Tyr
         45
                         50
Arg Ala Cys Pro Cys Leu Arg Asn Leu Thr Cys Ile Tyr Ser Lys Asn
                      65
Glu Lys Trp Leu Ser Ile Ala Tyr Gly Arg Cys Gln Lys Ile Gly Arg
                   80
Gln Lys Leu Ala Lys Lys Met Phe Phe
                95
<210> 180
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<210> 180 <211> 59 <212> PRT

<213> Homo sapiens

<400> 180

Met Ile Leu Cys Phe Leu Leu Pro His His Arg Leu Gln Glu Ala Arg

<210> 181 <211> 86 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -14..-1 <400> 181 Met Val Ala Leu Asn Leu Ile Leu Val Pro Cys Cys Ala Ala Trp Cys -5 -10 Asp Pro Arg Arg Ile His Ser Gln Asp Asp Val Pro Arg Ser Ser Ala 10 Ala Asp Thr Gly Ser Ala Met Gln Arg Arg Glu Ala Trp Ala Gly Trp 25 30 Arg Arg Ser Gln Pro Phe Ser Val Gly Leu Pro Ser Ala Glu Arg Leu 40 45 Glu Asn Gln Pro Gly Lys Leu Ser Trp Arg Ser Leu Val Gly Glu Gly . . 60 55 Tyr Arg Ile Cys Asp Leu 70

<210> 182 <211> 165 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -58..-1

<400> 182 Met Thr Arg Leu Cys Leu Pro Arg Pro Glu Ala Arg Glu Asp Pro Ile -55 -50 Pro Val Pro Pro Arg Gly Leu Gly Ala Gly Glu Gly Ser Gly Ser Pro -35 -30 Val Arg Pro Pro Val Ser Thr Trp Gly Pro Ser Trp Ala Gln Leu Leu -15 -20 Asp Ser Val Leu Trp Leu Gly Ala Leu Gly Leu Thr Ile Gln Ala Val -10 -5 1 Phe Ser Thr Thr Gly Pro Ala Leu Leu Leu Leu Val Ser Phe Leu 10 Thr Phe Asp Leu Leu His Arg Pro Ala Gly His Thr Leu Pro Gln Arg 25 30 Lys Leu Leu Thr Arg Gly Gln Ser Gln Gly Ala Gly Glu Gly Pro Gly 45 Gln Gln Glu Ala Leu Leu Gln Met Gly Thr Val Ser Gly Gln Leu 55 60 65 Ser Leu Gln Asp Ala Leu Leu Leu Leu Leu Met Gly Leu Gly Pro Leu

```
80
                                             85
              75
 Leu Arg Ala Cys Gly Met Pro Leu Thr Leu Leu Gly Leu Ala Phe Cys
       90 95
 Leu His Pro Trp Ala
   105
 <210> 183
 <211> 80
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -35..-1
 <400> 183
 Met Pro Phe Gln Phe Gly Thr Gln Pro Arg Arg Phe Pro Val Glu Gly
 -35 -30 -25 -20
Gly Asp Ser Ser Ile Glu Leu Glu Pro Gly Leu Ser Ser Ala Ala
           -15 -10 -5
 Cys Asn Gly Lys Glu Met Ser Pro Thr Arg Gln Leu Arg Arg Cys Pro
         1 5
                               10
 Gly Ser His Cys Leu Thr Ile Thr Asp Val Pro Val Thr Val Tyr Ala
                           25
       20
 Thr Thr Arg Lys Pro Pro Ala Gln Ser Ser Lys Glu Met His Pro Lys
        35
                        40
 <210> 184
 <211> 73
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -21..-1
 <400> 184
 Met Ala Pro Gln Thr Leu Leu Pro Val Leu Val Leu Cys Val Leu Leu
  -20 -15 -10
 Leu Gln Ala Gln Gly Gly Tyr Arg Asp Lys Met Arg Met Gln Arg Ile
                             5
 -5
                 1
 Lys Val Cys Glu Lys Arg Pro Ser Ile Asp Leu Cys Ile His His Cys
               20
           15
 Ser Cys Phe Gln Lys Cys Glu Thr Asn Lys Ile Cys Cys Ser Ala Phe
                      35 . 40
 Cys Gly Asn Ile Cys Met Ser Ile Leu
    45
 <210> 185
 <211> 98
 <212> PRT
 <213> Homo sapiens
 Met Leu Gly Ala Glu Thr Glu Glu Lys Leu Phe Asp Ala Pro Leu Ser
```

5

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 Ile
 Ser
 Lys
 Arg
 Glu
 Glu
 Leu
 Glu
 Glu
 Glu
 Val
 Pro
 Glu
 Asn
 Tyr
 Phe

 Tyr
 Val
 Pro
 Asp
 Leu
 Gly
 Glu
 Val
 Pro
 Glu
 Ile
 Asp
 Val
 Pro
 Ser
 Tyr

 Leu
 Pro
 Asp
 Leu
 Pro
 Gly
 Ile
 Ala
 Asp
 Leu
 Met
 Tyr
 Ile
 Ala
 Asp

 Leu
 Gly
 Pro
 Gly
 Ile
 Ala
 Pro
 Ser
 Ala
 Pro
 Gly
 Thr
 Ile
 Ala
 Asp

 For
 Thr
 Pro
 His
 Thr
 Glu
 Val
 Ala
 Glu
 Pro
 Leu
 Lys
 Thr
 Tyr
 Lys
 Met

 For
 Tyr
 Fro
 Fro
 Fro
 Leu
 Lys
 Thr
 Tyr
 Lys
 Met

 For
 Tyr
 Fro
 Fro
 Fro
 Fro
 Fro
 Fro
 Fro
 Fro
 Fro
 F

<210> 186 <211> 112 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1 <400> 186 Met Glu Ser Arg Val Leu Leu Arg Thr Phe Cys Leu Ile Phe Gly Leu -15 -10 Gly Ala Val Trp Gly Leu Gly Val Asp Pro Ser Leu Gln Ile Asp Val Leu Thr Glu Leu Glu Leu Gly Glu Ser Thr Thr Gly Val Arg Gln Val 20 Pro Gly Leu His Asn Gly Thr Lys Ala Phe Leu Phe Gln Asp Thr Pro 40 . 35 Arg Ser Ile Lys Ala Ser Thr Ala Thr Ala Glu Gln Phe Phe Gln Lys 55 50 Leu Arg Asn Lys His Glu Phe Thr Ile Leu Val Thr Leu Lys Gln Thr 70 65 His Leu Asn Ser Gly Val Ile Leu Ser Ile His His Leu Asp His Arg

80

<210> 187 <211> 70

85

<212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -44..-1 <400> 187 Met Cys Cys Tyr Cys Arg Ile Phe Cys Leu Arg Cys Thr Tyr Phe Pro -35 -40 Val His Cys Gly Met Cys Asn Leu Arg Tyr Phe Glu Phe Ser Thr Phe -20 -25 Leu Leu Ser Leu Ser Leu Ile Thr Tyr Cys Phe Trp Asp Pro Pro His -5 1 Arg Gly Ser His Ser Leu Ser Leu Glu His Thr Pro Leu Asp Phe Leu 15 Glu Trp Gly Leu Leu Arg

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<210> 188
<211> 92
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -13..-1
<400> 188
Met Leu Phe Ser Leu Ser Leu Leu Ser Asn Leu Asn Gln Ile Gly Ser
        -10
                            - 5
Ser His Leu Asp Arg Pro His Ile Pro Gly Gln Ser Ala Gln Leu Phe
                  10
Ile Tyr Gln Met Ser Ser Gln Gln Leu Gln Gln Gln Pro Ser Ala Asn
              25
                                  30
Lys Lys Ala Gly Lys Ile His Asn Thr Pro Phe Ala Asn Gln Leu Asn
                               45
             40
Pro Thr Gln His Leu Ala Lys Pro Phe Gln Gln Ile Leu Pro Gly Arg
                           60
         55
Gln Ser Gly Ser Leu Thr Ser Pro Phe Leu Ala Cys
<210> 189
<211> 207
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -42..-1
<400> 189
Met His Ile Leu Gln Leu Leu Thr Thr Val Asp Asp Gly Ile Gln Ala
   -40 -35 -30
Ile Val His Cys Pro Asp Thr Gly Lys Asp Ile Trp Asn Leu Leu Phe
                                     -15
                     -20
Asp Leu Val Cys His Glu Phe Cys Gln Ser Asp Asp Pro Pro Ile Ile
                                1
-10
              -5
Leu Gln Glu Gln Lys Thr Val Leu Ala Ser Val Phe Ser Val Leu Ser
                         15
Ala Ile Tyr Ala Ser Gln Thr Glu Gln Glu Tyr Leu Lys Ile Glu Lys
   25 30
                                   35
Val Asp Leu Pro Leu Ile Asp Ser Leu Ile Arg Val Leu Gln Asn Met
                                    50
              4.5
Glu Gln Cys Gln Lys Lys Pro Glu Asn Ser Ala Glu Ser Asn Thr Glu
                                  65 . 70
           60
Glu Thr Lys Arg Thr Asp Leu Thr Gln Asp Asp Leu His Leu Lys Ile
                               80
Leu Lys Asp Ile Leu Cys Glu Phe Leu Ser Asn Ile Phe Gln Ala Leu
                            95
Thr Lys Glu Thr Val Ala Gln Gly Val Lys Glu Gly Gln Leu Ser Lys
                        110
                                           115
     105
Gln Lys Cys Ser Ser Ala Phe Gln Asn Leu Leu Pro Phe Tyr Ser Pro
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140

Val Val Glu Asp Phe Ile Lys Ile Leu Arg Glu Val Asp Lys Ala Leu

Alæ Asp Asp Leu Glu Lys Asn Phe Pro Ser Leu Lys Val Gln Thr

130

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<211> 201
<212> PRT
<213 > Homo sapiens
<400> 190
Met Gln Val Ala Leu Lys Glu Asp Leu Asp Ala Leu Lys Glu Lys Phe
                                  10
Arg Thr Met Glu Ser Asn Gln Lys Ser Ser Phe Gln Glu Ile Pro Lys
                              25
Leu Asn Glu Glu Leu Leu Ser Lys Gln Lys Gln Leu Glu Lys Ile Glu
                          40
Ser Gly Glu Met Gly Leu Asn Lys Val Trp Ile Asn Ile Thr Glu Met
                      55
Asn Lys Gln Ile Ser Leu Leu Thr Ser Ala Val Asn His Leu Lys Ala
                                     75
Asn Val Lys Ser Ala Ala Asp Leu Ile Ser Leu Pro Thr Thr Val Glu
                                  90
Gly Leu Gln Lys Ser Val Ala Ser Ile Gly Asn Thr Leu Asn Ser Val
                              105
His Leu Ala Val Glu Ala Leu Gln Lys Thr Val Asp Glu His Lys Lys
                          120
Thr Met Glu Leu Gln Ser Asp Met Asn Gln His Phe Leu Lys Glu
                     135
                                         140
```

Thr Pro Gly Ser Asn Gln Ile Ile Pro Ser Pro Ser Ala Thr Ser Glu

Leu Asp Asn Lys Thr His Ser Glu Asn Leu Lys Gln Met Gly Asp Arg

165 170 Ser Ala Thr Leu Lys Arg Gln Ser Leu Asp Gln Val Thr Asn Arg Thr 180 185

145 150 155

Asp Thr Val Lys Ile Gln Lys Lys 195 200

<210> 191

<210> 190

<211> 379

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -37..-1

<400> 191

Met Pro His Ser Ser Leu His Pro Ser Ile Pro Cys Pro Arg Gly His -35 -30

Gly Ala Gln Lys Ala Ala Leu Val Leu Leu Ser Ala Cys Leu Val Thr -15 -10

Leu Trp Gly Leu Gly Glu Pro Pro Glu His Thr Leu Arg Tyr Leu Val 1 5

Leu His Leu Ala Ser Leu Gln Leu Gly Leu Leu Asn Gly Val Cys 20

Ser Leu Ala Glu Glu Leu Arg His Ile His Ser Arg Tyr Arg Gly Ser 35

Tyr Trp Arg Thr Val Arg Ala Cys Leu Gly Cys Pro Leu Arg Arg Gly 50

Ala Leu Leu Leu Ser Ile Tyr Phe Tyr Tyr Ser Leu Pro Asn Ala

70 60 65 Val Gly Pro Pro Phe Thr Trp Met Leu Ala Leu Leu Gly Leu Ser Gln 80 85 Ala Leu Asn Ile Leu Leu Gly Leu Lys Gly Leu Ala Pro Ala Glu Ile 100 Ser Ala Val Cys Glu Lys Gly Asn Phe Asn Val Ala His Gly Leu Ala 115 Trp Ser Tyr Tyr Ile Gly Tyr Leu Arg Leu Ile Leu Pro Glu Leu Gln 130 Ala Arg Ile Arg Thr Tyr Asn Gln His Tyr Asn Asn Leu Leu Arg Gly 145 150 Ala Val Ser Gln Arg Leu Tyr Ile Leu Leu Pro Leu Asp Cys Gly Val 165 160 Pro Asp Asn Leu Ser Met Ala Asp Pro Asn Ile Arg Phe Leu Asp Lys 180 175 Leu Pro Gln Gln Thr Gly Asp Arg Ala Gly Ile Lys Asp Arg Val Tyr 195 200 Ser Asn Ser Ile Tyr Glu Leu Leu Glu Asn Gly Gln Arg Ala Gly Thr 210 Cys Val Leu Glu Tyr Ala Thr Pro Leu Gln Thr Leu Phe Ala Met Ser 225 230 Gln Tyr Ser Gln Ala Gly Phe Ser Arg Glu Asp Arg Leu Glu Gln Ala 240 245 Lys Leu Phe Cys Arg Thr Leu Glu Asp Ile Leu Ala Asp Ala Pro Glu 260 255 Ser Gln Asn Asn Cys Arg Leu Ile Ala Tyr Gln Glu Pro Ala Asp Asp 275 Ser Ser Phe Ser Leu Ser Gln Glu Val Leu Arg His Leu Arg Gln Glu 295 290 Glu Lys Glu Glu Val Thr Val Gly Ser Leu Lys Thr Ser Ala Val Pro 300 305 310 Ser Thr Ser Thr Met Ser Gln Glu Pro Glu Leu Leu Ser Gly Met 320 325 Gly Lys Pro Leu Pro Leu Arg Thr Asp Phe Ser 335

<210> 192 <211> 112 <212> PRT <213> Homo sapiens

<400> 192

 Met
 Pro
 Ser
 Glu
 Gly
 Arg
 Cys
 Trp
 Glu
 Thr
 Leu
 Lys
 Ala
 Leu
 Arg
 Ser

 Ser
 Asp
 Lys
 Gly
 Arg
 Leu
 Cys
 Tyr
 Tyr
 Arg
 Asp
 Trp
 Leu
 Arg
 Arg

```
<211> 43
<212> PRT
<213> Homo sapiens
<400> 193
Ser Leu Pro Gln Ala Leu Trp Phe Gln Phe Phe Tyr His Ser Gly Ser
1
Ser Leu Glu Ser Pro Gly Met Leu Asn Gly Pro Phe Gln His Arg Asn
                            25
Ser Arg Ile Met Thr His Arg Ser Ala Glu Lys
<210> 194
<211> 51
<212> PRT
<213> Homo sapiens
<221> SIGNAL
<222> -16..-1
<400> 194
Met Leu Arg Ile Ala Leu Thr Leu Ile Pro Ser Met Leu Ser Arg Ala
 -15 -10 -5
Ala Gly Trp Cys Trp Tyr Lys Glu Pro Thr Gln Gln Phe Ser Tyr Leu
                                10
           5
Cys Leu Pro Cys Leu Ser Trp Asn Lys Lys Gly Asn Val Leu Gln Leu
 20
                  25
Pro Asn Phe
 35
<210> 195
<211> 244
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -18..-1
<400> 195
Met Ala Asn Pro Lys Leu Leu Gly Leu Glu Leu Ser Glu Ala Glu Ala
         -15 -10
Ile Gly Ala Asp Ser Ala Arg Phe Glu Glu Leu Leu Gln Ala Ser
      1
Lys Glu Leu Gln Gln Ala Gln Thr Thr Arg Pro Glu Ser Thr Gln Ile
                  20
                                    25
Gln Pro Gln Pro Gly Phe Cys Ile Lys Thr Asn Ser Ser Glu Gly Lys
                                 40
              35
Val Phe Ile Asn Ile Cys His Ser Pro Ser Ile Pro Pro Pro Ala Asp
                             55
Val Thr Glu Glu Leu Leu Gln Met Leu Glu Glu Asp Gln Ala Gly
Phe Arg Ile Pro Met Ser Leu Gly Glu Pro His Ala Glu Leu Asp Ala
Lys Gly Gln Gly Cys Thr Ala Tyr Asp Val Ala Val Asn Ser Asp Phe
```

100 105 110

Tyr Arg Arg Met Gln Asn Ser Asp Phe Leu Arg Glu Leu Val Ile Thr

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```
115
                                120
Ile Ala Arg Glu Gly Leu Glu Asp Ile Tyr Asn Leu Gln Leu Asn Pro
       130 135
Glu Trp Arg Met Met Lys Asn Arg Pro Phe Met Gly Ser Ile Ser Gln
                       150
                                           155
Gln Asn Ile Arg Ser Glu Gln Arg Pro Arg Ile Gln Glu Leu Gly Asp
                    165 170
Leu Tyr Thr Pro Ala Pro Gly Arg Ala Glu Ser Gly Pro Glu Lys Pro
                 180
                                   185
His Leu Asn Leu Trp Leu Glu Ala Pro Asp Leu Leu Leu Ala Glu Val
              195
                               200
Asp Leu Pro Lys Leu Asp Gly Ala Leu Gly Leu Ser Leu Glu Ile Gly
Arg Thr Ala Trp
       225
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<210> 196 <211> 353 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -34..-1

<400> 196 Met Glu Arg Gly Leu Lys Ser Ala Asp Pro Arg Asp Gly Thr Gly Tyr -25 -30 Thr Gly Trp Ala Gly Ile Ala Val Leu Tyr Leu His Leu Tyr Asp Val -10 Phe Gly Asp Pro Ala Tyr Leu Gln Leu Ala His Gly Tyr Val Lys Gln 10 Ser Leu Asn Cys Leu Thr Lys Arg Ser Ile Thr Phe Leu Cys Gly Asp 20 . 25 Ala Gly Pro Leu Ala Val Ala Ala Val Leu Tyr His Lys Met Asn Asn 35 40 Glu Lys Gln Ala Glu Asp Cys Ile Thr Arg Leu Ile His Leu Asn Lys 55 Ile Asp Pro His Ala Pro Asn Glu Met Leu Tyr Gly Arg Ile Gly Tyr 70 Ile Tyr Ala Leu Leu Phe Val Asn Lys Asn Phe Gly Val Glu Lys Thr 85 90 Pro Gln Ser His Ile Gln Gln Ile Cys Glu Thr Ile Leu Thr Ser Gly 105 110 100 Glu Asn Leu Ala Arg Lys Arg Asn Phe Thr Ala Lys Ser Pro Leu Met 115 120 Tyr Glu Trp Tyr Gln Glu Tyr Tyr Val Gly Ala Ala His Gly Leu Ala 130 135 Gly Ile Tyr Tyr Leu Met Gln Pro Ser Leu Gln Val Ser Gln Gly 150 Lys Leu His Ser Leu Val Lys Pro Ser Val Asp Tyr Val Cys Gln Leu 165 170 Lys Phe Pro Ser Gly Asn Tyr Pro Pro Cys Ile Gly Asp Asn Arg Asp 180 185 Leu Leu Val His Trp Cys His Gly Ala Pro Gly Val Ile Tyr Met Leu 195 200 Ile Gln Ala Tyr Lys Val Phe Arg Glu Glu Lys Tyr Leu Cys Asp Ala 215 220 210 Tyr Gln Cys Ala Asp Val Ile Trp Gln Tyr Gly Leu Leu Lys Lys Gly 230 **2**25

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```
Tyr Gly Leu Cys His Gly Ser Ala Gly Asn Ala Tyr Ala Phe Leu Thr
                    245
Leu Tyr Asn Leu Thr Gln Asp Met Lys Tyr Leu Tyr Arg Ala Cys Lys
                                   265
                260
Phe Ala Glu Trp Cys Leu Glu Tyr Gly Glu His Gly Cys Arg Thr Pro
                               280
             275
Asp Thr Pro Phe Ser Leu Phe Glu Gly Met Ala Gly Thr Ile Tyr Phe
                           295
         290
Leu Ala Asp Leu Leu Val Pro Thr Lys Ala Arg Phe Pro Ala Phe Glu
                                   315
              310
Leu
<210> 197
<211> 30
<212> PRT
<213> Homo sapiens
<400> 197
Met Gln Met Asp Thr Phe Phe Met Ser Glu Lys His Thr His Thr His
                     10
1 5
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Thr His Ile His Thr His Thr Arg Lys Thr Lys Lys Lys 20 25

<210> 198 <211> 112 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -48..-1

<400> 198 Met Gln Asp Thr Gly Ser Val Val Pro Leu His Trp Phe Gly Phe Gly -40 Tyr Ala Ala Leu Val Ala Ser Gly Gly Ile Ile Gly Tyr Val Lys Ala -25 Gly Ser Val Pro Ser Leu Ala Ala Gly Leu Leu Phe Gly Ser Leu Ala -10 Gly Leu Gly Ala Tyr Gln Leu Ser Gln Asp Pro Arg Asn Val Trp Val 10 5 Phe Leu Ala Thr Ser Gly Thr Leu Ala Gly Ile Met Gly Met Arg Phe 25 Tyr His Ser Gly Lys Phe Met Pro Ala Gly Leu Ile Ala Gly Ala Ser 40 Leu Leu Met Val Ala Lys Val Gly Val Ser Met Phe Asn Arg Pro His

<210> 199 <211> 54 <212> PRT <213> Homo sapiens <400> 199 Glu Ile Ala Gly Tyr Gly Ala Glu Gly Phe Ser Ser Val Leu Gly Tyr WO 99/31236 -143 - PCT/IB98/02122 .

```
        Pro
        Arg
        Trp
        His
        Arg
        Leu
        Pro
        Pro
        Gln
        Ser
        Leu
        Gln
        His
        Gln
        Tyr

        20
        25
        30

        Cys
        Gln
        Arg
        Arg
        Trp
        Pro
        Arg
        Arg
        Cys
        Leu
        Gln
        Ser
        His
        Thr
        Gln

        Ser
        Ser
        Gly
        His
        Leu
        Pro
        45
```

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<211> 151
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 200
Met Ala Ala Ser Thr Ser Met Xaa Pro Val Ala Val Thr Ala Ala Val
 -20 -15 -10
Ala Pro Val Leu Ser Ile Asn Ser Asp Phe Ser Asp Leu Arg Glu Ile
-5
            1 5
Lys Lys Gln Leu Leu Ile Ala Gly Leu Thr Arg Glu Arg Gly Leu
            20
                                25
      15
Leu His Ser Ser Lys Trp Ser Ala Glu Leu Ala Phe Ser Leu Pro Ala
                   35
Leu Pro Xaa Gly Gln Leu Gln Pro Pro Pro Pro Ile Thr Glu Glu Asp
                 50 ..55
Ala Gln Asp Met Asp Ala Tyr Thr Leu Ala Lys Ala Tyr Phe Asp Val
                    70 75
               65
Lys Glu Tyr Asp Arg Ala Ala His Phe Leu His Gly Cys Asn Ser Lys
                 85
            80
Lys Ala Tyr Phe Leu Tyr Met Tyr Ser Arg Tyr Leu Val Arg Ala Ile
         95
                         100
Leu Lys Cys His Ser Ala Phe Ser Glu Thr Ser Ile Phe Arg Thr Asn
   110 115
Gly Lys Val Lys Ser Phe Lys
   125
```

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<210> 201

<211> 228

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -25..-1

<400> 201

Met Ser Met Ala Val Glu
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<210> 200

```
Leu Met Ile Thr Ala Ile Leu Leu Gly Phe Leu Gly Leu Leu Gly
                              65
             60
Ile Ala Gly Leu Arg Cys Thr Asn Ile Gly Gly Leu Glu Leu Ser Arg
                          80
Lys Ala Lys Leu Ala Ala Thr Ala Gly Ala Pro His Ile Leu Ala Gly
                              100
                       95
Ile Cys Gly Met Val Ala Ile Ser Trp Tyr Ala Phe Asn Ile Thr Arg
                                   115
                   110
  105
Asp Phe Phe Asp Pro Leu Tyr Pro Gly Thr Lys Tyr Glu Leu Gly Pro
                125
                                130
Ala Leu Tyr Leu Gly Trp Ser Ala Ser Leu Ile Ser Ile Leu Gly Gly
                            145 150
             140
Leu Cys Leu Cys Ser Ala Cys Cys Cys Gly Ser Asp Glu Asp Pro Ala
         155
                        160
                                 165
Ala Ser Ala Arg Arg Pro Tyr Gln Ala Pro Val Ser Val Met Pro Val
                              180
                      175
Ala Thr Ser Asp Gln Glu Gly Asp Ser Ser Phe Gly Lys Tyr Gly Arg
                            195
                   190
Asn Ala Tyr Val
200
```

<211> 64 <212> PRT <213> Homo sapiens <220> <221> SIGNAL. <222> -47..-1 <400> 202 Met His Gly Phe Glu Ile Ile Ser Leu Lys Glu Glu Ser Pro Leu Gly -35 -40 Lys Val Ser Gln Gly Pro Leu Phe Asn Val Thr Ser Gly Ser Ser -25 -20 Pro Val Thr Trp Leu Gly Leu Leu Ser Phe Gln Asn Leu His Cys Phe -15 -10 -5 Pro Asp Leu Pro Thr Glu Met Pro Leu Arg Ala Lys Gly Val Asn Thr

<210> 202

5

Val Tyr Tyr Leu Ile Gln Lys Phe His Ser Arg Ala Leu Tyr Tyr Lys

5 10 15

Leu Ala Val Glu Gln Leu Gln Ser His Pro Glu Ala Gln Glu Ala Leu
20 25 30

<210> 204 <211> 87 <212> PRT <213> Homo sapiens

<400> 204

<210> 205
<211> 40
<212> PRT
<213> Homo sapiens

<220>
<221> SIGNAL
<222> -27..-1

<400> 205

<210> 206 <211> 154 <212> PRT <213> Homo sapiens

<400> 206
Met Gly Ser Leu Ser Gly Leu Arg Leu Ala Ala Gly Ser Cys Phe Arg

10 Leu Cys Glu Arg Asp Val Ser Ser Ser Leu Arg Leu Thr Arg Ser Ser 25 20 Asp Leu Lys Arg Ile Asn Gly Phe Cys Thr Lys Pro Gln Glu Ser Pro 40 4.5 Gly Ala Pro Ser Arg Thr Tyr Asn Arg Val Pro Leu His Lys Pro Thr 55 60 Asp Trp Gln Lys Lys Ile Leu Ile Trp Ser Gly Arg Phe Lys Lys Glu 75 70 Asp Glu Ile Pro Glu Thr Val Ser Leu Glu Met Leu Asp Ala Ala Lys 90 85 Asn Lys Met Arg Val Lys Ser Ser Tyr Leu Met Ile Ala Leu Thr Val 100 105 Val Gly Cys Ile Phe Met Val Ile Glu Gly Lys Lys Ala Ala Gln Arg 115 120 His Glu Thr Leu Thr Ser Leu Asn Leu Glu Lys Lys Ala Arg Leu Lys 135 Glu Glu Ala Ala Met Lys Ala Lys Thr Glu 150

<210> 207 <211> 101 <212> PRT <213> Homo sapiens

<400> 207 Met Val Cys Glu Lys Cys Glu Lys Lys Leu Gly Thr Val Ile Thr Pro 10 Asp Thr Trp Lys Asp Gly Ala Arg Asn Thr Thr Glu Ser Gly Gly Arg 25 Lys Leu Asn Lys Asn Lys Ala Leu Thr Ser Lys Lys Ala Arg Phe Asp 40 45 Pro Tyr Gly Lys Asn Lys Phe Ser Thr Cys Arg Ile Cys Lys Ser Ser 60 Val His Gln Pro Gly Ser His Tyr Cys Gln Gly Cys Ala Tyr Lys Lys 70 75 Gly Ile Cys Ala Met Cys Gly Lys Lys Val Leu Asp Thr Lys Asn Tyr 90 85 Lys Gln Thr Ser Val 100

<210> 208 <211> 456 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -22..-1

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Glu Glu Glu Glu Glu Arg Lys Lys Cys Pro Lys Lys Ala Ser
                    50 55
Phe Ala Ser Ala Ser Ala Glu Val Gly Lys Lys Gly Lys Lys Cys
               65
Gln Lys Gln Gly Pro Pro Cys Ser Asp Ser Glu Glu Glu Val Glu Arg
                            85
Lys Lys Lys Cys His Lys Gln Ala Leu Val Gly Ser Asp Ser Ala Glu
                          100
            95
Asp Glu Lys Arg Lys Arg Lys Cys Gln Lys His Ala Pro Ile Asn Ser
         110
                      115
Ala Gln His Leu Asp Asn Val Asp Gln Thr Gly Pro Lys Ala Trp Lys
      125 130 135
Gly Ser Thr Thr Asn Asp Pro Pro Lys Gln Ser Pro Gly Ser Thr Ser
                 145 150
Pro Lys Pro Pro His Thr Leu Ser Arg Lys Gln Trp Arg Asn Arg Gln
155 160 165
Lys Asn Lys Arg Arg Cys Lys Asn Lys Phe Gln Pro Pro Gln Val Pro
                 180 185
            175
Asp Gln Ala Pro Ala Glu Ala Pro Thr Glu Lys Thr Glu Val Ser Pro
                       195
       190
Val Pro Arg Thr Asp Ser His Gly Ala Arg Ala Gly Ala Leu Arg Ala
      205 210
Arg Met Ala Gln Arg Leu Asp Gly Ala Arg Phe Arg Tyr Leu Asn Glu
                225
Gln Leu Tyr Ser Gly Pro Ser Ser Ala Ala Gln Arg Leu Phe Gln Glu
               240
                             245
Asp Pro Glu Ala Phe Leu Leu Tyr His Arg Gly Phe Gln Ser Gln Val
            255
                         260
Lys Lys Trp Pro Leu Gln Pro Val Asp Arg Ile Ala Arg Asp Leu Arg
                        275 280
        270
Gln Arg Pro Ala Ser Leu Val Val Ala Asp Phe Gly Cys Gly Asp Cys
     285 290 295
Arg Leu Ala Ser Ser Ile Arg Asn Pro Val His Cys Phe Asp Leu Ala
                      310
                  305
Ser Leu Asp Pro Arg Val Thr Val Cys Asp Met Ala Gln Val Pro Leu
315 320 325 330
Glu Asp Glu Ser Val Asp Val Ala Val Phe Cys Leu Ser Leu Met Gly
                           340 345
   335
Thr Asn Ile Arg Asp Phe Leu Glu Glu Ala Asn Arg Val Leu Lys Pro
                       355 360
Gly Gly Leu Leu Lys Val Ala Glu Val Ser Ser Arg Phe Glu Asp Val
                     370 375
Arg Thr Phe Leu Arg Ala Val Thr Lys Leu Gly Phe Lys Ile Val Ser
                 385
                          390
Lys Asp Leu Thr Asn Ser His Phe Phe Leu Phe Asp Phe Gln Lys Thr
395 400 405 410
Gly Pro Pro Leu Val Gly Pro Lys Ala Gln Leu Ser Gly Leu Gln Leu
                          420 425
            415
Gln Pro Cys Leu Tyr Lys Arg Arg
         430
```

<210> 209 <211> 98 <212> PRT <213> Homo sapiens

<221> SIGNAL <222> -17..-1

 <400> 209

 Met Pro Ser Ser Phe Phe Leu Leu Leu Gln Phe Phe Leu Arg Ile Asp -15

 Gly Val Leu Ile Arg Met Asn Asp Thr Arg Leu Tyr His Glu Ala Asp 1

 Lys Thr Tyr Met Leu Arg Glu Tyr Thr Ser Arg Glu Ser Lys Ile Ser 20

 Ser Leu Met His Val Pro Pro Ser Leu Phe Thr Glu Pro Asn Glu Ile 35

 Ser Gln Tyr Leu Pro Ile Lys Glu Ala Val Cys Glu Lys Leu Ile Phe 50

 Pro Glu Arg Ile Asp Pro Asn Pro Ala Asp Ser Gln Lys Ser Thr Gln 65

 Val Glu 80

<210> 210 <211> 83 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -29..-1

<210> 211 <211> 229 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -23..-1

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```
50
Gly Lys Thr Leu Val Phe Glu Gln Arg Lys Ser Asp Gly Val His Thr
                         70
 60 65
Val Glu Thr Glu Val Gly Asp Tyr Met Phe Cys Phe Asp Asn Thr Phe
                  80
Ser Thr Ile Ser Glu Lys Val Ile Phe Phe Glu Leu Ile Leu Asp Asn
            95
                             100
Met Gly Glu Gln Ala Gln Glu Glu Asp Trp Lys Lys Tyr Ile Thr
          110
                           115
Gly Thr Asp Ile Leu Asp Met Lys Leu Glu Asp Ile Leu Glu Ser Ile
      125 130 135
Ser Ser Ile Lys Ser Arg Leu Ser Lys Ser Gly His Ile Gln Ile Leu
                           150
            145
Leu Arg Ala Phe Glu Ala Arg Asp Arg Asn Ile Gln Glu Ser Asn Phe
                         165
 155 160
Asp Arg Val Asn Phe Trp Ser Met Val Asn Leu Val Val Met Val Val
                   180
170 . 175
Val Ser Ala Ile Gln Val Tyr Met Leu Lys Ser Leu Phe Glu Asp Lys
           190
                           195
Arg Lys Ser Arg Thr
        205
```

<210> 212 <211> 152 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1

<400> 212

Met Ala Gln Leu Gly Ala Val Val Ala Val Ala Ser Ser Phe Phe Cys -10 -15 Ala Ser Leu Phe Ser Ala Val His Lys Ile Glu Glu Gly His Ile Gly 1 Val Tyr Tyr Arg Gly Gly Ala Leu Leu Thr Ser Thr Ser Gly Pro Gly 20 15 Phe His Leu Met Leu Pro Phe Ile Thr Ser Tyr Lys Ser Val Gln Thr 40 35 30 Thr Leu Gln Thr Asp Glu Val Lys Asn Val Pro Cys Gly Thr Ser Gly 50 Gly Val Met Ile Tyr Phe Asp Arg Ile Glu Val Val Asn Phe Leu Val 70 Pro Asn Ala Val His Asp Ile Val Lys Asn Tyr Thr Ala Asp Tyr Asp 85 Lys Ala Leu Ile Phe Asn Lys Ile His His Glu Leu Asn Gln Phe Cys 105 100 Ser Val His Thr Leu Gln Glu Val Tyr Ile Glu Leu Phe Gly Leu Glu 115 110 Asn Asp Phe Ser Gln Glu Ser Ser 130

<210> 213 <211> 179 <212> PRT <213 > Homo sapiens

Leu Leu Ser Leu Ser Gly Val Phe Ala Val His Lys Pro Lys Gly Pro

15 20 25

Thr Ser Ala Glu Leu Leu Asn Arg Leu Lys Glu Lys Leu Leu Ala Glu

30 40

Ala Gly Met Pro Ser Pro Glu Trp Thr Lys Arg Lys Lys Gln Thr Leu
45 50 55

Lys Ile Gly His Gly Gly Thr Leu Asp Ser Ala Ala Arg Gly Val Leu 60 65 70

Val Val Gly Ile Gly Ser Gly Thr Lys Met Leu Thr Ser Met Leu Ser

80

85

90

Gly Ser Lys Arg Tyr Thr Ala Ile Gly Glu Leu Gly Lys Ala Thr Asp 95 100 105

Thr Leu Asp Ser Thr Gly Lys Val Thr Glu Glu Lys Pro Tyr Gly Met 110 115 120

Asn Leu Ile 125

<210> 214

<211> 269

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -92..-1

<400> 214

Met Ile Thr His Val Thr Leu Glu Asp Ala Leu Ser Asn Val Asp Leu -90 -85 -80

Leu Glu Glu Leu Pro Leu Pro Asp Gln Gln Pro Cys Ile Glu Pro Pro
-75 -70 -65

Pro Ser Ser Ile Met Tyr Gln Ala Asn Phe Asp Thr Asn Phe Glu Asp -60 -55 -50 -45

Arg Asn Ala Phe Val Thr Gly Ile Ala Arg Tyr Ile Glu Gln Ala Thr
-40 -35 -30

Val His Ser Ser Met Asn Glu Met Leu Glu Glu Gly His Glu Tyr Ala
-25 -20 -15

Val Met Leu Tyr Thr Trp Arg Ser Cys Ser Arg Ala Ile Pro Gln Val

-10 -5 1
Lys Cys Asn Glu Gln Pro Asn Arg Val Glu Ile Tyr Glu Lys Thr Val
5 10 15 20

Glu Val Leu Glu Pro Glu Val Thr Lys Leu Met Lys Phe Met Tyr Phe
25 30 35

Gln Arg Lys Ala Ile Glu Arg Phe Cys Ser Glu Val Lys Arg Leu Cys
40 45 50

His Ala Glu Arg Arg Lys Asp Phe Val Ser Glu Ala Tyr Leu Leu Thr
55 60 65

```
Leu Gly Lys Phe Ile Asn Met Phe Ala Val Leu Asp Glu Leu Lys Asn
         75
Met Lys Cys Ser Val Lys Asn Asp His Ser Ala Tyr Lys Arg Ala Ala
                    95
       90
Gln Phe Leu Arg Lys Met Ala Asp Pro Gln Ser Ile Gln Glu Ser Gln
            105 110
Asn Leu Ser Met Phe Leu Ala Asn His Asn Arg Ile Thr Gln Cys Leu
        120 125 130
His Gln Gln Leu Glu Val Ile Pro Gly Tyr Glu Glu Leu Leu Ala Asp
                     140
Ile Val Asn Ile Cys Val Asp Tyr Tyr Glu Asn Lys Met Tyr Leu Thr
  150 155
                          160
Pro Ser Glu Lys His Met Leu Leu Lys Val Lys Leu Pro
               170
                               175
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<210> 215

<211> 135 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -22..-1 <400> 215 Met Gln Thr Val Tyr Tyr Gly Ser Leu Gly Leu Trp Leu Ala Leu Val -15 -10 Asp Gly Leu Val Arg Ser Ser Pro Ser Leu Asp Gln Met Phe Asp Ala 5 1 Glu Ile Leu Gly Phe Ser Thr Pro Pro Gly Arg Leu Ser Met Met Ser 20 Phe Ile Phe Asn Ala Leu Thr Cys Ala Leu Gly Leu Leu Tyr Phe Ile 35 40 Arg Arg Gly Lys Gln Cys Leu Asp Phe Thr Val Thr Val His Phe Phe 50 55 His Leu Leu Gly Cys Trp Phe Tyr Ser Ser Arg Phe Pro Ser Ala Leu 65 Thr Trp Trp Leu Val Gln Ala Val Cys Ile Ala Leu Met Ala Val Ile 85

Gly Glu Tyr Leu Cys Met Arg Thr Glu Leu Lys Glu Ile Pro Leu Asn

95

Ser Ala Pro Lys Ser Asn Val

<210> 217

60

<210> 218

<211> 125 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -54..-1 <400> 217 Met Ala Asp Glu Glu Leu Glu Ala Leu Arg Arg Gln Arg Leu Ala Glu -50 -45 Leu Gln Ala Lys His Gly Asp Pro Gly Asp Ala Ala Gln Gln Glu Ala -30 -25 Lys His Arg Glu Ala Glu Met Arg Asn Ser Ile Leu Ala Gln Val Leu -15 -10 Asp Gln Ser Ala Arg Ala Arg Leu Ser Asn Leu Ala Leu Val Lys Pro 5 Glu Lys Thr Lys Ala Val Glu Asn Tyr Leu Ile Gln Met Ala Arg Tyr 15 20 Gly Gln Leu Ser Glu Lys Val Ser Glu Gln Gly Leu Ile Glu Ile Leu 35 Lys Lys Val Ser Gln Gln Thr Glu Lys Thr Thr Thr Val Lys Phe Asn 50

Arg Arg Lys Val Met Asp Ser Asp Glu Asp Asp Asp Tyr

65

<211> 376 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1 <400> 218 Met Gly His Arg Phe Leu Arg Gly Leu Leu Thr Leu Leu Pro Pro -15 Pro Pro Leu Tyr Thr Arg His Arg Met Leu Gly Pro Glu Ser Val Pro 1 Pro Pro Lys Arg Ser Arg Ser Lys Leu Met Ala Pro Pro Arg Ile Gly 15 20 Thr His Asn Gly Thr Phe His Cys Asp Glu Ala Leu Ala Cys Ala Leu 35 Leu Arg Leu Leu Pro Glu Tyr Arg Asp Ala Glu Ile Val Arg Thr Arg 50 Asp Pro Glu Lys Leu Ala Ser Cys Asp Ile Val Val Asp Val Gly Gly 70 65 Glu Tyr Asp Pro Arg Arg His Arg Tyr Asp His His Gln Arg Ser Phe 8.5 Thr Glu Thr Met Ser Ser Leu Ser Pro Gly Arg Pro Trp Gln Thr Lys

WO 99/31236 PCT/IB98/02122 -153-

```
100
         95
Leu Ser Ser Ala Gly Leu Ile Tyr Leu His Phe Gly His Lys Leu Leu
      110 115 120
Ala Gln Leu Leu Gly Thr Ser Glu Glu Asp Ser Met Val Gly Thr Leu
                   130
                            135
Tyr Asp Lys Met Tyr Glu Asn Phe Val Glu Glu Val Asp Ala Val Asp
                145
                                   150
Asn Gly Ile Ser Gln Trp Ala Glu Gly Glu Pro Arg Tyr Ala Leu Thr
             160
                               165 170
Thr Thr Leu Ser Ala Arg Val Ala Arg Leu Asn Pro Thr Trp Asn His
          175
                           180
Pro Asp Gln Asp Thr Glu Ala Gly Phe Lys Arg Ala Met Asp Leu Val
                        195
Gln Glu Glu Phe Leu Gln Arg Leu Asp Phe Tyr Gln His Ser Trp Leu
                     210
Pro Ala Arg Ala Leu Val Glu Glu Ala Leu Ala Gln Arg Phe Gln Val
                                   230
Asp Pro Ser Gly Glu Ile Val Glu Leu Ala Lys Gly Ala Cys Pro Trp
                               245
Lys Glu His Leu Tyr His Leu Glu Ser Gly Leu Ser Pro Pro Val Ala
                260
Ile Phe Phe Val Ile Tyr Thr Asp Gln Ala Gly Gln Trp Arg Ile Gln
      270 275
                                280
Cys Val Pro Lys Glu Pro His Ser Phe Gln Ser Arg Leu Pro Leu Pro
                     290
                                     295
Glu Pro Trp Arg Gly Leu Arg Asp Glu Ala Leu Asp Gln Val Ser Gly
                 305
                                  310
Ile Pro Gly Cys Ile Phe Val His Ala Ser Gly Phe Ile Gly Gly His
             320
                               325 . 330
Arg Thr Arg Glu Gly Ala Leu Ser Met Ala Arg Ala Thr Leu Ala Gln
          335
                           340 345
Arg Ser Tyr Leu Pro Gln Ile Ser
      350
```

<210> 219 <211> 211 <212> PRT

<213> Homo sapiens

<221> SIGNAL <222> -30..-1

<220>

Met Gly Glu Ala Ser Pro Pro Ala Pro Ala Arg Arg His Leu Leu Val -25 -20 Leu Leu Leu Leu Ser Thr Leu Val Ile Pro Ser Ala Ala Ala Pro -10 **-** 5 Ile His Asp Ala Asp Ala Gln Glu Ser Ser Leu Gly Leu Thr Gly Leu 10 Gln Ser Leu Leu Gln Gly Phe Ser Arg Leu Phe Leu Lys Gly Asn Leu 25 30 Leu Arg Gly Ile Asp Ser Leu Phe Ser Ala Pro Met Asp Phe Arg Gly 40 45 Leu Pro Gly Asn Tyr His Lys Glu Glu Asn Gln Glu His Gln Leu Gly 55 60 Asn Asn Thr Leu Ser Ser His Leu Gln Ile Asp Lys Val Pro Arg Met 75 Glu Glu Lys Glu Ala Leu Val Pro Ile Gln Lys Ala Thr Asp Ser Phe

```
His Thr Glu Leu His Pro Arg Val Ala Phe Trp Ile Ile Lys Leu Pro
                 105
                                110
Arg Arg Arg Ser His Gln Asp Ala Leu Glu Gly Gly His Trp Leu Ser
                     125
115 120
Glu Lys Arg His Arg Leu Gln Ala Ile Arg Asp Gly Leu Arg Lys Gly
               140 145
           135
Thr His Lys Asp Val Leu Glu Glu Gly Thr Glu Ser Ser Ser His Ser
       150 155 160
Arg Leu Ser Pro Arg Lys Thr His Leu Leu Tyr Ile Leu Arg Pro Ser
            170
                           175
Arg Gln Leu
  180
```

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<211> 154
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -60..-1
<400> 220
Met Gly Ser Lys Cys Cys Lys Gly Gly Pro Asp Glu Asp Ala Val Glu
-60 -55 -50
Arg Gln Arg Arg Gln Lys Leu Leu Leu Ala Gln Leu His His Arg Lys
                           -35 ·· -30
            -40
Arg Val Lys Ala Ala Gly Gln Ile Gln Ala Trp Trp Arg Gly Val Leu
         -25 -20 -15
Val Arg Arg Thr Leu Leu Val Ala Ala Leu Arg Ala Trp Met Ile Gln
      -10 -5
Cys Trp Trp Arg Thr Leu Val Gln Arg Arg Ile Arg Gln Arg Arg Gln
                              15
   10
Ala Leu Leu Arg Val Tyr Val Ile Gln Glu Gln Ala Thr Val Lys Leu
           25 30
Gln Ser Cys Ile Arg Met Trp Gln Cys Arg Gln Cys Tyr Arg Gln Met
                       45
```

Cys Asn Ala Leu Cys Leu Phe Gln Val Pro Glu Ser Ser Leu Ala Phe

Gln Thr Asp Gly Phe Leu Gln Val Gln Tyr Ala Ile Pro Ser Lys Gln

75

-20

55 60

Pro Glu Phe His Ile Glu Ile Leu Ser Ile

<210> 220

WO 99/31236 -155- PCT/IB98/02122 .

<210> 222 <211> 346 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -19..-1 <400> 222 Met Ala Met Ala Gln Lys Leu Ser His Leu Leu Pro Ser Leu Arg Gln -15 -10 -5 Val Ile Gln Glu Pro Gln Leu Ser Leu Gln Pro Glu Pro Val Phe Thr Val Asp Arg Ala Glu Val Pro Pro Leu Phe Trp Lys Pro Tyr Ile Tyr 20 Ala Gly Tyr Arg Pro Leu His Gln Thr Trp Arg Phe Tyr Phe Arg Thr 35 40 Leu Phe Gln Gln His Asn Glu Ala Val Asn Val Trp Thr His Leu Leu 50 5.5 Ala Ala Leu Val Leu Leu Leu Arg Leu Ala Leu Phe Val Glu Thr Val 70 Asp Phe Trp Gly Asp Pro His Ala Leu Pro Leu Phe Ile Ile Val Leu 85 Ala Ser Phe Thr Tyr Leu Ser Leu Ser Ala Leu Ala His Leu Leu Gln 100 105 Ala Lys Ser Glu Phe Trp His Tyr Ser Phe Phe Phe Leu Asp Tyr Val 115 120 Gly Val Ala Val Tyr Gln Phe Gly Ser Ala Leu Ala His Phe Tyr Tyr 130 135 Ala Ile Glu Pro Ala Trp His Ala Gln Val Gln Ala Val Phe Leu Pro 150 Met Ala Ala Phe Leu Ala Trp Leu Ser Cys Ile Gly Ser Cys Tyr Asn 165 170 Lys Tyr Ile Gln Lys Pro Gly Leu Leu Gly Arg Thr Cys Gln Glu Val 180 175 Pro Ser Val Leu Ala Tyr Ala Leu Asp Ile Ser Pro Val Val His Arg 195 200 Ile Phe Val Ser Ser Asp Pro Thr Thr Asp Asp Pro Ala Leu Leu Tyr 215 210 His Lys Cys Gln Val Val Phe Phe Leu Leu Ala Ala Ala Phe Phe Ser 230 Thr Phe Met Pro Glu Arg Trp Phe Pro Gly Ser Cys His Val Phe Gly 245 Gln Gly His Gln Leu Phe His Ile Phe Leu Val Leu Cys Thr Leu Ala 260

Gln Leu Glu Ala Val Ala Leu Asp Tyr Glu Ala Arg Arg Pro Ile Tyr

```
270
                  275
                                   280
Glu Pro Leu His Thr His Trp Pro His Asn Phe Ser Gly Leu Phe Leu
                      295
             290
Leu Thr Val Gly Ser Ser Ile Leu Thr Ala Phe Leu Leu Ser Gln Leu
                            310
          305
Val Gln Arg Lys Leu Asp Gln Lys Thr Lys
                         325
<210> 223
<211> 210
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -20..-1
<400> 223
Met Asp Asn Arg Phe Ala Thr Ala Phe Val Ile Ala Cys Val Leu Ser
               -15
                                 -10
Leu Ile Ser Thr Ile Tyr Met Ala Ala Ser Ile Gly Thr Asp Phe Trp
                           5
                                           10
            1
Tyr Glu Tyr Arg Ser Pro Val Gln Glu Asn Ser Ser Asp Leu Asn Lys
                        20
    15
Ser Ile Trp Asp Glu Phe Ile Ser Asp Glu Ala Asp Glu Lys Thr Tyr
           35
                                      40
Asn Asp Ala Leu Phe Arg Tyr Asn Gly Thr Val Gly Leu Trp Arg Arg
       . 50
                                   55
Cys Ile Thr Ile Pro Lys Asn Met His Trp Tyr Ser Pro Pro Glu Arg
                               70
              65
Thr Glu Ser Phe Asp Val Val Thr Lys Cys Val Ser Phe Thr Leu Thr
                                             90
          80
                            85
Glu Gln Phe Met Glu Lys Phe Val Asp Pro Gly Asn His Asn Ser Gly
      95 ·
                        100
                                         105
Ile Asp Leu Leu Arg Thr Tyr Leu Trp Arg Cys Gln Phe Leu Leu Pro
                    115
                                      120
Phe Val Ser Leu Gly Leu Met Cys Phe Gly Ala Leu Ile Gly Leu Cys
                 130
                                   135
Ala Cys Ile Cys Arg Ser Leu Tyr Pro Thr Ile Ala Thr Gly Ile Leu
              145
                               150
His Leu Leu Ala Val Thr Lys Glu Ser Met Leu Pro Ala Gly Ala Glu
                                             170
          160
                           165
Ser Lys His Thr Ala Thr Pro Ala His Ala Cys Val Gln Thr Gly Lys
                        180
Pro Lys
   190
<210> 224
<211> 184
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -20..-1
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<400> 224

Met Asp Asn Arg Phe Ala Thr Ala Phe Val Ile Ala Cys Val Leu Ser

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```
-20
Leu Ile Ser Thr Ile Tyr Met Ala Ala Ser Ile Gly Thr Asp Phe Trp
Tyr Glu Tyr Arg Ser Pro Val Gln Glu Asn Ser Ser Asp Leu Asn Lys
                           20
Ser Ile Trp Asp Glu Phe Ile Ser Asp Glu Ala Asp Glu Lys Thr Tyr
Asn Asp Ala Pro Phe Arg Tyr Asn Gly Thr Val Gly Leu Trp Arg Arg
Cys Ile Thr Ile Pro Lys Asn Met His Trp Tyr Ser Pro Pro Glu Arg
Thr Glu Ser Phe Asp Val Val Thr Lys Cys Val Ser Phe Thr Leu Thr
Glu Gln Phe Met Glu Lys Phe Val Asp Pro Gly Asn His Asn Ser Gly
                          100
Ile Asp Leu Leu Arg Thr Tyr Leu Trp Arg Cys Gln Phe Leu Leu Pro
                                        120
Phe Val Ser Leu Gly Leu Met Cys Phe Gly Ala Leu Ile Gly Leu Cys
            130
Ala Cys Ile Cys Arg Ser Leu Tyr Pro Thr Ile Ala Thr Gly Ile Leu
              145
                                  150
His Leu Leu Ala Asp Thr Met Leu
           160
```

<210> 225 <211> 227 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -22..-1

<400> 225

Met Gly Trp Thr Met Arg Leu Val Thr Ala Ala Leu Leu Gly Leu -15 Met Met Val Val Thr Gly Asp Glu Asp Glu Asn Ser Pro Cys Ala His 1 Glu Ala Leu Leu Asp Glu Asp Thr Leu Phe Cys Gln Gly Leu Glu Val 15 20 Phe Tyr Pro Glu Leu Gly Asn Ile Gly Cys Lys Val Val Pro Asp Cys 35 Asn Asn Tyr Arg Gln Lys Ile Thr Ser Trp Met Glu Pro Ile Val Lys 50 Phe Pro Gly Ala Val Asp Gly Ala Thr Tyr Ile Leu Val Met Val Asp 70 65 Pro Asp Ala Pro Ser Arg Ala Glu Pro Arg Gln Arg Phe Trp Arg His 80 85 Trp Leu Val Thr Asp Ile Lys Gly Ala Asp Leu Lys Lys Gly Lys Ile 95 100 Gln Gly Gln Glu Leu Ser Ala Tyr Gln Ala Pro Ser Pro Pro Ala His 115 110 Ser Gly Phe His Arg Tyr Gln Phe Phe Val Tyr Leu Gln Glu Gly Lys 130 135 Val Ile Ser Leu Leu Pro Lys Glu Asn Lys Thr Arg Gly Ser Trp Lys 145 150 Met Asp Arg Phe Leu Asn Arg Phe His Leu Gly Glu Pro Glu Ala Ser 165 160 Thr Gln Phe Met Thr Gln Asn Tyr Gln Asp Ser Pro Thr Leu Gln Ala 180

Pro Arg Glu Arg Ala Ser Glu Pro Lys His Lys Asn Gln Ala Glu Ile 190 195 Ala Ala Cys 205 <210> 226 <211> 74 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -41..-1 <400> 226 Met Ile Ala Arg Arg Asn Pro Val Pro Leu Arg Phe Leu Pro Asp Glu -40 -35 -30 Ala Arg Ser Leu Pro Pro Pro Lys Leu Thr Asp Pro Arg Leu Leu Tyr -20 . -15 -25 Ile Gly Phe Leu Gly Tyr Cys Ser Gly Leu Ile Asp Asn Leu Ile Arg 1 5 - 5 Arg Arg Pro Ile Ala Thr Ala Gly Leu His Arg Gln Leu Leu Tyr Ile 15 10 Thr Ala Phe Phe Leu Leu Asp Ile Ile Leu 25 30 <210> 227 <211> 73 <212> PRT <213> Homo sapiens <400> 227 Met Glu Lys Tyr Glu Asn Leu Gly Leu Val Gly Glu Gly Ser Tyr Gly 10 5 Met Val Met Lys Cys Arg Asn Lys Asp Thr Gly Arg Ile Val Ala Ile 20 25 Lys Lys Phe Leu Glu Ser Asp Asp Lys Met Val Lys Lys Ile Ala 40 45 Met Arg Glu Val Lys Leu Leu Lys Gln Leu Arg His Glu Asn Leu Val 55 Asn Leu Leu Glu Val Cys Lys Lys <210> 228 <211> 82 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -16..-1

Met Lys Arg Leu Leu Pro Ala Thr Ser Leu Ala Gly Pro Val Leu Ser

Thr Leu Ile Ala Pro Thr Pro Met Leu Phe Cys Glu Asp Lys Ser Trp

-5

-10

<400> 228

-15

WO 99/31236 -159- PCT/IB98/02122 -

```
5
                             10
Asp Leu Phe Leu Phe Phe Lys Ser His Lys Thr Trp Gly Ile Ser Thr
                 25
Asn Leu Ser Ser Cys Pro Phe Gly Asn Leu Phe Leu Cys Val Gln Phe
                    40
Val Arg Glu Lys Gln Ser Phe Cys Met Asn Thr Glu Cys Asp Leu Arg
Lys Asn
65
<210> 229
<211> 119
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -56..-1
<400> 229
Met Ala Glu Pro Ser Ala Ala Thr Gln Ser His Ser Ile Ser Ser Ser
                 -50
Ser Phe Gly Ala Glu Pro Ser Ala Pro Gly Gly Gly Ser Pro Gly
          -35
                       -30
Ala Cys Pro Ala Leu Gly Thr Lys Ser Cys Ser Ser Ser Cys Ala Asp
           -20 -15 -10
Ser Phe Val Ser Ser Ser Ser Gln Pro Val Ser Leu Phe Ser Thr
       -5 1 5
Ser Gln Glu Gly Leu Ser Ser Leu Cys Ser Asp Glu Pro Ser Ser Glu
10 15 20
Ile Met Thr Ser Ser Phe Leu Ser Ser Ser Glu Ile His Asn Thr Gly
       30 35
Leu Thr Ile Leu His Gly Glu Lys Ser His Val Leu Gly Ser Gln Pro
                    . 50
             45
Ile Leu Ala Lys Lys Lys
         60
<210> 230
<211> 54
<212> PRT
<213> Homo sapiens
Ala Phe Val Trp Glu Pro Ala Met Val Arg Ile Asn Ala Leu Thr Ala
                              10
Ala Ser Glu Ala Ala Cys Leu Ile Val Ser Val Asp Glu Thr Ile Lys
                          25
Asn Pro Arg Ser Thr Val Asp Ala Pro Thr Ala Ala Gly Arg Gly Arg
                      40
```

<210> 231 <211> 210 <212> PRT <213> Homo sapiens

50

Gly Arg Gly Arg Pro His

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Trp Gly Ala Glu Lys Gly Glu Ser Pro Glu Val Ser Ser Phe Glu Thr
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Arg Leu Ala Asn Met Ala Lys Pro Cys Leu Tyr
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Met Ser Ala Arg Ile Pro Phe Tyr Lys Asp Thr Ser Gln Ile Arg Leu
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Gly Ser Thr Ile Ile Pro His Phe Asn Leu Ile Thr Phe Val Lys Thr
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Phe Phe Gln Ile
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Leu Glu Ser Pro Ile Asp Pro Gln Pro Leu Ser Phe Lys Glu Pro Pro
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                                         15
Leu Leu Gly Val Leu His Pro Asn Thr Lys Leu Arg Gln Ala Glu
                                      30
Arg Leu Phe Glu Asn Gln Leu Val Gly Pro Glu Ser Ile Ala His Ile
                                  45
Gly Asp Val Met Phe Thr Gly Thr Ala Asp Gly Arg Val Val Lys Leu
Glu Asn Gly Glu Ile Glu Thr Ile Ala Arg Phe Gly Ser Gly Pro Cys
                          75
Lys Thr Arg Asp Asp Glu Pro Val Cys Gly Arg Pro Leu Gly Ile Arg
                      90
                                         95
Ala Gly Pro Asn Gly Thr Leu Phe Val Ala Asp Ala Cys Lys Gly Leu
                  105
                                      110
Phe Glu Val Asn Pro Trp Lys Arg Glu Val Lys Leu Leu Ser Ser
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125

Glu Thr Pro Ile Glu Gly Lys Asn Met Ser Phe Val Asn Asp Leu Thr

140

120

Val Ser Gln Asp Gly Arg Lys Ile Tyr Phe Thr Asp Ser Ser Ser Lys 155 Trp Gln Arg Arg Asp Tyr Leu Leu Leu Val Met Glu Gly Thr Asp Asp 170 175 Gly Arg Leu Leu Glu Tyr Asp Thr Val Thr Arg Glu Val Lys Val Leu 185 Leu Asp Gln Leu Arg Phe Pro Asn Gly Val Gln Leu Ser Pro Ala Glu 200 205 Asp Phe Val Leu Val Ala Glu Thr Thr Met Ala Arg Ile Arg Arg Val 215 220 Tyr Val Ser Gly Leu Met Lys Gly Gly Ala Asp Leu Phe Val Glu Asn 235 240 Met Pro Gly Phe Pro Asp Asn Ile Arg Pro Ser Ser Ser Gly Gly Tyr 250 255 Trp Val Gly Met Ser Thr Ile Arg Pro Asn Pro Gly Phe Ser Met Leu 265 270 Asp Phe Leu Ser Glu Arg Pro Trp Ile Lys Arg Met Ile Phe Lys Ala 285 Lys Lys Lys

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1
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Gln Leu Ser Asp Lys Val His Asn Asp Ile
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Leu Ile Ser Thr Ile Tyr Met Ala Ala Ser Ile Gly Thr Asp Phe Trp
              1
Tyr Glu Tyr Arg Ser Pro Val Gln Glu Asn Ser Ser Asp Leu Asn Lys
     15
                         20
Ser Ile Trp Asp Glu Phe Ile Ser Asp Glu Ala Asp Glu Lys Thr Tyr
                     35
Asn Asp Ala Leu Phe Arg Tyr Asn Gly Thr Val Gly Leu Trp Gly Arg
               50
                        .... 55
Cys Ile Thr Ile Pro Lys Asn Met His Trp Tyr Ser Pro Pro Glu Arg
              65
                                 70
Thr Gly Ile Ser Leu Ile Leu Thr Ser Val Phe Phe Thr Trp Leu Ile
          80
                    85
Ile Asp Lys Thr Thr
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Gln His Xaa Xaa Ala Xaa Xaa Leu Leu Val Phe Asn Phe Leu Leu Ile
                      -15
                                         -10
Leu Thr Ile Leu Thr Ile Trp Leu Phe Lys Asn His Arg Phe Arg Phe
                  1
                                5
Leu His Glu Thr Gly Gly Ala Met Val Tyr Gly Leu Ile Met Gly Leu
                              20
Ile Ser Arg Tyr Ala Thr Ala Pro Thr Asp Ile Glu Ser Gly Thr Val
                          35
Cys Asp Cys Val Lys Leu Thr Phe Ser Pro Pro Thr Leu Leu Val Asn
                      50
                                         55
Val Thr Asp Gln Val Tyr Glu Tyr Lys Tyr Lys Arg Glu Ile Ser Gln
                  65
                                    70
His Asn Ile Asn Pro His Gln Gly Asn Ala Ile Leu Glu Lys Met Thr
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85

Phe Asp Pro Glu Ile Phe Phe Asn Val Leu Leu Pro Pro Ile Ile Phe

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100
His Ala Gly Tyr Ser Leu Lys Lys Arg His Phe Phe Gln Asn Leu Gly
 110 115 120
Ser Ile Leu Thr Tyr Ala Phe Leu Gly Thr Ala Ile Ser Cys Ile Val
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Ile Gly
140
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Val Leu Ala Leu Gly Phe Leu Gly Cys Tyr Gly Ala Lys Thr Glu Ser
                             1 5
               <del>-</del> 5
Met Cys Ala Leu Val Thr Phe Phe Phe Ile Leu Leu Leu Ile Phe Ile
          10 15 20
Ala Glu Val Ala Ala Ala Val Val Ala Leu Val Tyr Thr Thr Met Ala
        25 30 35
Glu His Phe Leu Thr Leu Leu Val Val Pro Ala Ile Lys Lys Asp Tyr
     40 45 50
Gly Ser Gln Glu Asp Phe Thr Gln Val Trp Asn Thr Thr Met Lys Gly
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                                65
Leu Lys Cys Arg Gly Phe Thr Asn Tyr Thr Asp Phe Glu Asp Ser Pro
              75
                            80
Tyr Phe Lys Met His Lys Pro Val Thr Met Lys Lys Lys
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Val Met Leu Thr Thr Gln Leu Leu Pro Ser Lys Tyr Cys Asp Leu Leu
            -95
                 - 90
His Lys Ser Ala Ala His Leu Gly Lys Trp Gln Lys Leu Glu His Gly
                       -75
Ser Tyr Ser Asn Ala Pro Gln His Ile Trp Ser Glu Asn Thr Ile Trp
                     -60
Pro Gln Gly Val Leu Val Arg His Ser Arg Cys Leu Tyr Arg Ala Met
 -50 -45 -40
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Gly Pro Tyr Asn Val Ala Val Pro Ser Asp Val Ser His Ala Arg Phe
-35 -25 -20
Tyr Phe Leu Phe His Arg Pro Leu Arg Leu Leu Asn Leu Leu Ile Leu

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-15
                                      -10
                                                          - 5
  Ile Glu Gly Gly Val Val Phe Tyr Gln Leu Tyr Ser Leu Leu Arg Ser
              1
                       5
                                                  10
  Glu Lys Trp Asn His Thr Leu Ser Met Ala Leu Ile Leu Phe Cys Asn
     15
                          20
  Tyr Tyr Val Leu Phe Lys Leu Leu Arg Asp Arg Ile Val Leu Gly Arg
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                    Met Pro Ser Val Asn Ser Ala Gly Leu Cys Val
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                                         -15
 ttg cag ttg aca acg gca gtr acc agt gcc ttt tta cta gca aaa gtg
                                                                        98
 Leu Gln Leu Thr Thr Ala Val Thr Ser Ala Phe Leu Leu Ala Lys Val
                 - 5
                                     1
 aat cct ttc gaa rct ttt ctc tca agg ggc ttt tgg cta tgt gcc
                                                                       146
 Asn Pro Phe Glu Xaa Phe Leu Ser Arg Gly Phe Trp Leu Cys Ala Ala
                             15
                                                 2.0
 cat cat ttc att cat cct tgc ctg gat tgagacgtgt tcctgattca
                                                                       193
 His His Phe Ile His Pro Cys Leu Asp
                         30
 aagtgttacc tcaagaagca gaagaagaaa acagactcct gatagttcag gatgcttcag
                                                                       253
 agagggcagc acttatacct ggtggtcttt ctgatggtca gttttattcc cctcctgaat
                                                                       313
 ccgaagcagg atctgaagaa gctgaagaaa aacaggacag tgagaaacca cttttagaac
                                                                       373
 tatgagtact acttttgtta aatgtgaaaa accctcacag aaagtcatcg aggcaaaaag
                                                                       433
 aggcaggcag tggagtctcc ctgtcgacag taaagttgaa atggtgacgt ccactgctgg
                                                                       493
 Ctttattgaa cagctaataa agatttattt attgtaatac ctcacagacg ttgtaccata
                                                                       553
 tccatgcaca tttagttgcc tgcctgtggc tggtaaggta atgtcatgat tcatcctctc
                                                                       613
 ttcagtgaga ctgagcctga tgtgttaaca aataggtgaa gaaagtcttg tgctgtattc
                                                                       673
 Ctaatcaaaa gacttaatat attgaagtaa cactttttta gtaagcaaga taccttttta
                                                                      733
 tttcaattca cagaatggaa tttttttgtt tcatgtctca gatttatttt gtatttcttt
                                                                       793
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tttaacactc tacatttccc ttgtttttta actcatgcac atgtgctctt tgtacagttt

taaaaagtgt aataaaatct gacatgtcaa araaaaaaaa mcy

853

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actgtgggco gtgaaataaa	gcctgcctgc gcccaagcac	tgatgtggg tgggaaaaa	c tctaggccag a aaaaaa	cttgttgtca	cgtacgtggt	81 85
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scor	peptide 130 Heijne matr e`3.599999 AFTLXSLLQAA	0463257				
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-5	a Ala Leu Le	eu Cys Val 1	aac gcc atc Asn Ala Ile 5	Ala Val Leu	His Glu 10	160
GIU Arg Ph	e Leu Lys As 15	sn Ile Gly	tgg gga aca Trp Gly Thr 20	Asp Gln Gly	Ile Gly 25	208
GIY Phe GI	y Glu Glu Pi 30	co Gly Ile	aaa tca sag Lys Ser Xaa 35	Xaa Met Xaa 40	Leu Ile	256
Arg Ser Va.	l Arg Thr Va	al Met Arg ' 50	gtg cca ttg Val Pro Leu	Ile Ile Val	Asn Ser	304
60	e Val Leu Le	eu Leu Leu 1 65	_			354
atatettage	aaraggacat tggctgacct aaaaaaaaaa	tgcacttgtc	kttattactt aaaaatgtaa	tggtcattat t agctgaaaat a	ggaatattt aaaaccaggg	414 474 495

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<222> 21..614

<221> sig_peptide

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<221> polyA site
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tgaggagctg gagctggtgg ggactgggcc gca atg gac aag ctg aag aag gtg
                                                                      114
                                     Met Asp Lys Leu Lys Lys Val
ctg agc ggg cag gac acg gag gac cgg agc ggc ctg tcc gag gtt gtt
                                                                      162
Leu Ser Gly Gln Asp Thr Glu Asp Arg Ser Gly Leu Ser Glu Val Val
            -45
                                -40
gag gca tct tca tta agc tgg agt acc agg ata aaa ggc ttc att gcg
                                                                      210
Glu Ala Ser Ser Leu Ser Trp Ser Thr Arg Ile Lys Gly Phe Ile Ala
        -30
                            -25
                                                -20
tgt ttt gct ata gga att ctc tgc tca ctg ctg ggt act gtt ctg ctg
                                                                      258
Cys Phe Ala Ile Gly Ile Leu Cys Ser Leu Leu Gly Thr Val Leu Leu
                        -10
                                            -5
tgg gtg ccc agg aag gga cta cac ctc ttc gca gtg ttt tat acc ttt
                                                                      306
Trp Val Pro Arg Lys Gly Leu His Leu Phe Ala Val Phe Tyr Thr Phe
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ggt aat atc gca tca att ggg agt acc atc ttc ctc atg gga cca gtg
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Gly Asn Ile Ala Ser Ile Gly Ser Thr Ile Phe Leu Met Gly Pro Val
                                25
aaa cag ctg aag cga atg ttt gag cct act cgt ttg att gca act atc
                                                                      402
Lys Gln Leu Lys Arg Met Phe Glu Pro Thr Arg Leu Ile Ala Thr Ile
        35
                            40
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atg gtg ctg ttg tgt ttt gca ctt acc ctg tgt tct gcc ttt tgg tgg
                                                                      450
Met Val Leu Cys Phe Ala Leu Thr Leu Cys Ser Ala Phe Trp Trp
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cat aac aag gga ctt gca ctt atc ttc tgc att ttg cag tct ttg gca
                                                                      498
His Asn Lys Gly Leu Ala Leu Ile Phe Cys Ile Leu Gln Ser Leu Ala
65
                    70
                                        75
ttg acg tgg tac agc ctt tcc ttc ata cca ttt gca agg gat gct gtg
                                                                      546
Leu Thr Trp Tyr Ser Leu Ser Phe Ile Pro Phe Ala Arg Asp Ala Val
                85
                                    90
aaa aad tgt ttt gcc gtg tgt ctt gca taattcatgg ccagttttat
                                                                      593
Lys Xaa Cys Phe Ala Val Cys Leu Ala
            100
gaagetttgg aaggeactat ggacagaage tggtggacag ttttgtwact atettegaaa
                                                                      653
cctctgtctt acagacatgt gccttttatc ttgcagcaat gtgttgcttg tgattcgaac
                                                                      713
atttgagggt tacttttgga agcaacaata cattctcgaa cctgaatgtc agtagcacag
                                                                      773
gatgagaagt gggttctgta tcttgtggag tggaatcttc ctcatgtacc tgtttcctct
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aaaa
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<222> 507..518
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              Met Lys Ala Leu Cys Leu Leu Leu Pro Val Leu
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ggg ctg ttg gtg tct agc aag acc ctg tgc tcc atg gaa gaa gcc atc
Gly Leu Leu Val Ser Ser Lys Thr Leu Cys Ser Met Glu Glu Ala Ile
aat gag agg atc cag gag gtc gcc ggc tcc cta ata ttt agg gca ata
                                                                  205
Asn Glu Arg Ile Gln Glu Val Ala Gly Ser Leu Ile Phe Arg Ala Ile
               15
                                  20
age age att gge ega ggg age gag age gte ace tee agg ggg gae etg
                                                                  253
Ser Ser Ile Gly Arg Gly Ser Glu Ser Val Thr Ser Arg Gly Asp Leu
           30
                              35
                                                 40
get act tgc ccc cga ggc ttc gcc gtc acc ggc tgc act tgt ggc tcc
                                                                  301
Ala Thr Cys Pro Arg Gly Phe Ala Val Thr Gly Cys Thr Cys Gly Ser
      45
                          50
gcc tgt ggc tcg tgg gat gtg cgc gcc gag acc aca tgt cac tgc cag
                                                                  349
Ala Cys Gly Ser Trp Asp Val Arg Ala Glu Thr Thr Cys His Cys Gln
                      65
                                          70
                                                                  397
tgc gcg ggc atg gac tgg acc gga gcg cgc tgc tgt cgt gtg cag ccc
Cys Ala Gly Met Asp Trp Thr Gly Ala Arg Cys Cys Arg Val Gln Pro
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                                      85
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518
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<211> 350

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<223> Von Heijne matrix

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Phe Leu Xaa Leu Met Thr Leu Thr Thr His Val His Ser Ser Ala Lys

cca aat gaa caa ccc tgg ttg ttg aac tagcacctaa ggtcttarat

- 5

ggtacgcgtt gctatacaga atctttggat atgtgcatca gtggtttatg ccaaattgtt

211

271

-10

Pro Asn Glu Gln Pro Trp Leu Leu Asn

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natgggtcca cctgccggct ggtccgaggg cartataaat cccakctctc cgcaaccaaa
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ggtcctgatc acttatatct ggaarccawa accctccagg ggactaawgg tgaaaacagt
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ctcasctcca caggaacttt ccttgtggac aattctagtg tggacttcca gaawtttcca
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gacwdagaga tactgagaat ggctggacca ctcacagcag atttcattgt caawattcgt
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gccaggtcag tcaaatttgc tagttcattt gtcataaaca taactcaagt tccaaatagg
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aaaaa
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                                                                      104
Gly Arg Leu Cys Leu Leu Thr Ile Val Gly Leu Ile Leu Pro Thr Arg
                            -10
gga cag acg ttg aaa gat acc acg tcc agt tct tca gca gac tca act
                                                                      152
Gly Gln Thr Leu Lys Asp Thr Thr Ser Ser Ser Ser Ala Asp Ser Thr
                                        10
atc atg gac att cag gtc ccg aca cga gcc cca gat gca gtc tac aca
                                                                      200
Ile Met Asp Ile Gln Val Pro Thr Arg Ala Pro Asp Ala Val Tyr Thr
               20
gaa ctc cag ccc acc tct cca acc cca acc tgg cct gct gat gaa aca
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Glu Leu Gln Pro Thr Ser Pro Thr Pro Thr Trp Pro Ala Asp Glu Thr
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                                40
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Pro Gln Pro Gln Thr Gln Thr Gln Gln Leu Glu Gly Thr Asp Gly Pro
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cta gtg aca gat cca gag aca cac wak agc mcc aaa gca gct cat ccc
Leu Val Thr Asp Pro Glu Thr His Xaa Ser Xaa Lys Ala Ala His Pro
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                                            75
act gat gac acc acg acg ctc tct gag aga cca tcc cca agc aca kac
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Thr Asp Asp Thr Thr Thr Leu Ser Glu Arg Pro Ser Pro Ser Thr Xaa
                   85
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atg acc o	cct tct Pro Ser	tct atg	atg aac Met Asn	aca ccc	tcc qq	y Asn Xaa	g ggc tgt a Gly Cys	488
Trp Ser (cag ctg Gln Leu	tgc tgt Cys Cys	Ser Ser	120 cag gca Gln Ala	tca tca Ser Se	r Ser Ser	cca gtg Pro Val	536
gca agt g Ala Ser A	130 gca ggc Ala Gly	agc tgt Ser Cys	Pro Gly	tat gcc Tyr Ala	Gly Ile	e Ile Ala	ggt gag Gly Glu	584
tcc atc a	aga aac Arg Asn	Arg Ser	150 tgacaac	ctg ctgg	15: gcaccc (ıg	632
ggaagacad	ca gatga cc gcccc	tgaag c	tggagcca; ctacctgg:	g ggctgd c gccttg	cggt ccggg ctg	gagtetee gteeetea	ggccagagag tacctcccc agttatctcc	692 752 812 860
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-15 cga cct g Arg Pro V	al Leu (Gln Asn	-10 ctg ttg Leu Leu	Gln Ser	-5 cca ggc Pro Gly	ttg aca Leu Thr	Trp Ser	149
1 ttg gaa g Leu Glu V	tg ccc a	act ggg Thr Gly	aga gaa Arg Glu	Gly Lys	gaa ggt Glu Gly	Gly Asp	15 cgg gga Arg Gly	197
cca ggg c Pro Gly L	eu Xaa (ggg gcc 3ly Ala	act cca Thr Pro	25 gcc agg Ala Arg	agc cct Ser Pro	Gln Gly	aag gag Lys Glu	245
atg ggg a Met Gly A 50	ga caa a	agg acc Arg Thr	aga aag	gtg aag Val Lys	ggc cct Gly Pro 60	45 gct tgg Ala Trp	akt cac Xaa His	293

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Thr Ala Asn Gln Glu Leu Asn Arg Met Arg Ser Leu Ser Ser Gly Ser 65 70 75 80	341
gtg cca gtg ggg cat ctg gag ggt ggc acg gtc aag ctt cag aag gac Val Pro Val Gly His Leu Glu Gly Gly Thr Val Lys Leu Gln Lys Asp 85 90 95	389
acg ggc ctc cat tcc tgc ara gat ggt atg gct tct ctt gaa ggg acg Thr Gly Leu His Ser Cys Xaa Asp Gly Met Ala Ser Leu Glu Gly Thr	437
cca gct tca gtc ctg gct gat gct tgc cca gga ttc cat gat gtg aan Pro Ala Ser Val Leu Ala Asp Ala Cys Pro Gly Phe His Asp Val Xaa	485
gtt car arg gcc cta ttt ggg tta agt ggg ana rta ctg tgg ctg aaa Val Gln Xaa Ala Leu Phe Gly Leu Ser Gly Xaa Xaa Leu Trp Leu Lys	533
130 135 140 acc cac ttc tgc ctt tct att ana ctt taaataaact ctgaaracct Thr His Phe Cys Leu Ser Ile Xaa Leu	580
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ggaagcagca ccaagttcac ggccaacgcc ttggcactag ggtccaga atg gct aca	-
ggaagcagca ccaagttcac ggccaacgcc ttggcactag ggtccaga atg gct aca Met Ala Thr -55 aca gtc cct gat ggt tgc cgc aat ggc ctg aaa tcc aag tac tac aga Thr Val Pro Asp Gly Cys Arg Asn Gly Leu Lys Ser Lys Tyr Tyr Arg	117
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a+a		~~~				35					40					453
7.00	Dha	999	atc	CEC	דננ	tcc	atc	tgc	TTC	tcc	tgc	ctg	ctg	gct	cat	453
	Pne	Gly	TTE	ьeu		ser	ıте	Cys	Pne		Cys	ьеи	Leu	Ala		
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		agt														501
Ala	Val	Ser	Leu	Thr	Lys	Leu	Val	Arg	Gly	Arg	Lys	Ala	Pro	Phe	Pro	
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tat	cgc	tat	tgaa	atata	att o	atcci	tgac	ca to	qaata	agga	c caa	acat	caat			598
Tyr			•		•				•	33						
- 2 -		95														
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gago	aag	atg														169
														Glu		
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gaq	aaq	gaa	cct	cta	qca	qtc	gac	tcc	taa	taa	cta	gat		gac	cac	217
		Glu														
	_,,	-15					-10		P	11 P	ыeu	-5	-10	OLY	1110	
ac=	aca		ac-	~~~	aca	000		acc	ata	~~~	+ ~ +	_	+	at-	+++	265
		gtg														265
		Val	Ата	GIN		Pro	FLO	Ата	val		Ser	ser	ser	ьеи		
	1				5					10					15	
		tca														313
Asp	Leu	Ser	Val	Leu	Lys	Leu	His	His	Ser	Leu	Gln	Xaa	Ser	Xaa	Pro	
				~ ~					25					30		
				20					_							
gac	ctg	cgg	cac		gtg	ctg	gtc	atr	_	act	ctg	cgg	ċgc		cag	361

Asp	Leu	Arg	His 35	Leu	Val	Leu	Val	Xaa 40	Asn	Thr	Leu	Arg	Arg 45	Ile	Gln	
Ala	Ser	Met 50	Ala	Pro	Ala	gct Ala	Ala 55	Leu	Pro	Pro	Val	Pro 60	Thr	Pro	Pro	409
						gac Asp 70										457
						arm Xaa										505
						caa Gln										553
		Ile				ccg Pro										601
						cta Leu										649
	_		_			atg Met 150		-		_			_		_	697
						ggc Gly			-		_		_		_	745
						gcc Ala										793
			_	_	_	gag Glu	_	-	_				_			835
gaga gaga gggg	cetes agaca gages gecet	gaa a aga a ctg g	gete aagad ateta gaatt ggtea	acag agtco acco atago	ge to	ggctt ggcaa tagtg	ccct actto gatgo	ato agt aca aca aat ctt	acag atccg cgaca cctct	gaga gtcc aggg gat	tcct tctg	gggct ggtgg ggaag	tg g ca g	ggcca gggct actga	accaac actttg aggcag aattcc aatcag	895 955 1015 1075 1135 1182

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Met Glu Thr Leu Tyr Arg Val Pro Phe Leu Val Leu Glu Cys Pro Asn	
-100 -95 -90 -85	
ctg aag ctg aag aag ccg ccc tgg ttg cac atg ccg tcg gcc atg act	154
Leu Lys Leu Lys Lys Pro Pro Trp Leu His Met Pro Ser Ala Met Thr	
-80 -75 -70	
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Val Tyr Ala Leu Val Val Ser Tyr Phe Leu Ile Thr Gly Gly Ile	
-65 -60 -55	
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Ile Tyr Asp Val Ile Val Glu Pro Pro Ser Val Gly Ser Met Thr Asp	
-50 -45 -40	
gaa cat ggg cat cag agg cca gta gct ttc ttg gcc tac aga gta aat	298
Glu His Gly His Gln Arg Pro Val Ala Phe Leu Ala Tyr Arg Val Asn	
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gga caa tat att atg gaa gga ctt gca tcc agc ttc cta ttt aca atg	346
Gly Gln Tyr Ile Met Glu Gly Leu Ala Ser Ser Phe Leu Phe Thr Met	
-20 -15 -10 -5	
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Gly Gly Leu Gly Phe Ile Ile Leu Asp Gly Ser Asn Ala Pro Asn Ile	
1 5 10	
cca aaa ctc aat aga ttc ctt ctt ctg ttc att gga ttc gtc tgt gtc	442
Pro Lys Leu Asn Arg Phe Leu Leu Leu Phe Ile Gly Phe Val Cys Val	
15 20 25	
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Leu Xaa Ser Phe Xaa Xaa Ala Arg Val Phe Met Arg Met Lys Leu Pro	
30 35 .40	
ggc tat ctg atg ggt tagagtgcct ttgasaagaa atcagtggat actggatttg	545
Gly Tyr Leu Met Gly	
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                                                                       96
Leu Thr Pro Cys Leu Thr Val Pro Arg Arg Pro Leu Phe Leu Leu Leu
                                -25
cac ctg tgt ccc cat ctg ccc ttc ttg ttg ctc ctg tca tgt gtc ggg
                                                                      144
His Leu Cys Pro His Leu Pro Phe Leu Leu Leu Ser Cys Val Gly
       -15
                            -10
gke www ecc tee tgt etg ect tet tee tee act tgt gte age ttg cat
                                                                      192
Xaa Xaa Pro Ser Cys Leu Pro Ser Ser Ser Thr Cys Val Ser Leu His
                   5
                                       10
ttt ttt att oct gac tgagtcacca caccectete ceetgateaa agggaatatk
                                                                      247
Phe Phe Ile Pro Asp
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artttttaat ttggatcgac tgaggtgcca ggagaaactg cagkcccagg tatccmvaca
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gecaccagga tggtccctcg ccccacccc accgcctctk ccccaccttt tccaacgtgt
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                                                                      547
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                                                                      727
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             -30
                                 -25
                                                     -20
caa acc aat ctc att cta ttt tgt gtc ggt gct gtg ggc gcc tgt act
                                                                      98
Gln Thr Asn Leu Ile Leu Phe Cys Val Gly Ala Val Gly Ala Cys Thr
       - 15
                           -10
                                                - 5
                                                                     146
ctc tct gtc aca caa ccg tgg tac cta gaa gtg gac tac act cat gag
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Leu Ser Wal Thr Gln Pro Trp Tyr Leu Glu Val Asp Tyr Thr His Glu

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			35			Phe		40					45			
ctg	tgc	ttg	gac	a aa	tgc	aaa	agt	gag	gca	gas	aag	ttc	aca	gtg	agg	290
		50				Lys	55					60				
gag	gcc	ctc	aaa	gaa	aac	caa	gtt	tcc	.ctc	act	gta	aac	aga	gtg	act	338
	65					Gln 70					75					
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ser 80	Asn	Asp	ser	Ala	11e 85	Tyr	Ile	Cys	Gly		Ala	Phe	Pro	Ser		
	gaa	aca	arra	act		cag	202	~~~	~~~	90					95	424
Pro	Glu	Ala	Ara	Ala	Lvs	Gln	Thr	Glv	Glv	999 Glv	Thr	Thr	Leu	gra val	gca Val	434
			5	100	-75	0111		O ₁ y	105	Oly	1111	1111	пеп	110	Vai	
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Arg	Glu	Ile	Lys 115	Leu	Leu	Ser	Lys	Glu 120	Leu	Arg	Ser	Phe	Leu 125	Thr	Ala	
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	145					Lys 150					155					
aaa	gaa	gac	tca	caa	aag	aag	aag	agt	gct	cgg,	cgt	att	ttt	cag	gaa	626
பழ்த் 160	GIU	Asp	Ser	GIn	Lys 165	Lys	Lys	Ser	Ala		Arg	Ile	Phe	Gln		
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Ile	Ala	Gln	Glu	Leu	Tvr	His	Lvs	Ara	His	yrg Val	Glu	Thr	Acn	Cag	Gln	674
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Ser	Glu	Lys	Asp 195	Asn	Asn	Thr	Tyr	Glu 200	Asn	Arg	Arg	Val	Leu 205	Ser	Asn	
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Tyr	Glu	Arg 210	Pro													
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taat	akto	at t	acca	aaat	a ct	aaaa	ссса	aca	aaat	gca	acto	gaaaa	at a	cctt	ccaaa	954
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Thr Arg Val Glu Ser Glu Lys Cys Asn Asn Leu Trp Leu Phe Leu Glu	
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Thr Gly Gln Leu Pro Lys Asp Arg Ser Thr Asp Gln Xaa Ser 25 30 35	
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Leu Ser Tyr Leu Pro Leu Trp Leu Gly Pro Ile Trp Pro Cys Ser Gly	
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Ser Thr Leu Gly Lys Pro Asp Pro Gly Val Trp Pro Ser Leu Phe Arg	
5 10 15	
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Pro Trp Asp Ala Ala Ser Pro Gly Asn Tyr Ala Leu Ser Arg Gly Xaa 20 25 30 35	
aac cak tat gav aak tgg ggg cag ggc aca cat tca tct ttg	419
Asn Xaa Tyr Xaa Xaa Trp Gly Gln Gly Thr His Ser Ser Leu	
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ag atg ccc tgt cca acg tgg acc tgc ttg aag agc ttc ccc tcc ccg
  Met Pro Cys Pro Thr Trp Thr Cys Leu Lys Ser Phe Pro Ser Pro
                                 -10
              -15
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acc agc agc cat gca tcg agc ctc cac ctt cct cca tca tgt acc agg
Thr Ser Ser His Ala Ser Ser Leu His Leu Pro Pro Ser Cys Thr Arg
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cta act ttg aca caa act ttg agg aca gga atg cat ttg tca cgg gca
Leu Thr Leu Thr Gln Thr Leu Arg Thr Gly Met His Leu Ser Arg Ala
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                                          25
ttg caa ggt aca ttg acc agg cta cag tcc act cca gca tgaatgarat
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Leu Gln Gly Thr Leu Thr Arg Leu Gln Ser Thr Pro Ala
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                                       40
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cattccccag gtgaaatgca acragcagcc caaccgakta raratctatg araaracagt
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                                                                  1152
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                          -70
                                                                      100
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Ile Ser Ile Phe Pro Thr Met Met Val Cys Met Met Ala Trp Arg Pro
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                    -55
-60
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Ile Gln Ala Leu Met Ala Ile Ser Ala Thr Phe Lys Met Leu Glu Ser
                                    -35
                -40
tca agc cag aag ttt ctt cag ggt ttg gtc tat ctc att ggg aac ctg
Ser Ser Gln Lys Phe Leu Gln Gly Leu Val Tyr Leu Ile Gly Asn Leu
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                                -20
            -25
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                                                                      244
Met Gly Leu Ala Leu Ala Val Tyr Lys Cys Gln Ser Met Gly Leu Leu
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cct aca cat gca tcg gat tgg tta gcc ttc att gag ccc cct gag aga
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cct ggt ccc tat gta ttt ggg tct tat tta cat cct tct tta agc cca
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Pro Gly Pro Tyr Val Phe Gly Ser Tyr Leu His Pro Ser Leu Ser Pro
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                                45
gtg gct cct cag cat act ctt aaa cta atc act tat gtt aaa aaa aac
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Val Ala Pro Gln His Thr Leu Lys Leu Ile Thr Tyr Val Lys Lys Asn
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aaaaaacttt atttttgttt ccagtacaga gcaaaacaac aacaaaaaaa cataactatg
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                                                                      340
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Val Ala Tyr Cys Met Thr Thr Arg Thr Tyr Tyr Thr Pro Thr Arg Met
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Lys Val Ser Lys Ser Cys Val Pro Arg Cys Phe Glu Xaa Cys Val
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Cys Gly Ser Leu Leu Pro Gly Leu Trp Gln His Leu Thr Ala Asn His -10 1

tgg cct cca ttc tcc sct ttc ctc tgt aca gtt tgc tct ggt tcc tca Trp Pro Pro Phe Ser Xaa Phe Leu Cys Thr Val Cys Ser Gly Ser Ser 10 15 20	326
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Asn Lys Phe Gly Ala Glu Glu Xaa Ser Leu Ile Gly Leu Ser Gly Ile 5 10 15	
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Tyr Ser Glu Xaa Ser Ala Pro Xaa Phe Ala Ile Phe Asn Phe Val Gln	
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   Met Tyr Val Trp Pro Cys Ala Val Val Leu Ala Gln Tyr Leu Trp
                               -75
ttt cac aga aga tct ctg cca ggc aag gcc atc tta gag att gga gct
                                                                      155
Phe His Arg Arg Ser Leu Pro Gly Lys Ala Ile Leu Glu Ile Gly Ala
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                                                                      203
gga gtg agc ctt cca gga att ttg gct gcc aaa tgt ggt gca gaa gta
Gly Val Ser Leu Pro Gly Ile Leu Ala Ala Lys Cys Gly Ala Glu Val
                        -45
ata ctg tca gac agc tca gaa ctg cct cac tgt ctg gaa gtc tgt cgg
                                                                      251
Ile Leu Ser Asp Ser Ser Glu Leu Pro His Cys Leu Glu Val Cys Arg
                    -30
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caa agc tgc caa atg aat aac ctg cca cat ctg cag gtg gta gga cta
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Gln Ser Cys Gln Met Asn Asn Leu Pro His Leu Gln Val Val Gly Leu
                                     -10
                -15
aca tgg ggt cat ata tct tgg gat ctt ctg gct cta cca cca caa gat
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Thr Trp Gly His Ile Ser Trp Asp Leu Leu Ala Leu Pro Pro Gln Asp
att atc ctt gca tct gat gtg ttc ttt gaa cca gaa rat ttt gaa gac
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Ile Ile Leu Ala Ser Asp Val Phe Phe Glu Pro Glu Xaa Phe Glu Asp
                        20
att ttg gct aca ata tat ttt ttg atg cac aar aat ccc aag gtc caa
                                                                      443
Ile Leu Ala Thr Ile Tyr Phe Leu Met His Lys Asn Pro Lys Val Gln
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ttg tgg tct act tat caa gtt agg art gct gac tgg tca ctt gaa gct
Leu Trp Ser Thr Tyr Gln Val Arg Xaa Ala Asp Trp Ser Leu Glu Ala
tta ctc tac aaa tgg gat atg aaa tgt gtc cac att cct ctt gag tct
                                                                      539
Leu Leu Tyr Lys Trp Asp Met Lys Cys Val His Ile Pro Leu Glu Ser
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                                                                      587
ttt gat gca gac aaa gaa rat ata gca gaa tct acc ctt cca gga aga
Phe Asp Ala Asp Lys Glu Xaa Ile Ala Glu Ser Thr Leu Pro Gly Arg
cat aca gtt gaa atg ctg gtc att tcc ttt gca aag gac agt ctc
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His Thr Val Glu Met Leu Val Ile Ser Phe Ala Lys Asp Ser Leu
                        100
                                                                       692
tgaattatac ctacaacctg ttctgggaca gtatcaatac tgatgagcaa cctggcacac
aaactatgag cagaccactt cagcttgaga atgcagtggg tctgaagatg gtcaagtctg
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812

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                      Met Thr Ser Gly Gln Ala Arg Ala Ser Xaa Gln
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                                                       -100
tee eec cag gee etg gag gae teg gge eeg gtg aat ate tea gte tea
                                                                      101
Ser Pro Gln Ala Leu Glu Asp Ser Gly Pro Val Asn Ile Ser Val Ser
        -95
                            -90
                                                 -85
atc acc cta acc ctg gac cca ctg aaa ccc ttc gga ggg tat tcc cgc
                                                                      149
Ile Thr Leu Thr Leu Asp Pro Leu Lys Pro Phe Gly Gly Tyr Ser Arg
                        -75
                                            -70
aac gtc acc cat ctg tac tca acc atc tta ggg cat cag att gga ctt
                                                                      197
Asn Val Thr His Leu Tyr Ser Thr Ile Leu Gly His Gln Ile Gly Leu
                    -60
                                        -55
tca ggc agg gaa gcc cac gag gag ata aac atc acc ttc acc ctg cct
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Ser Gly Arg Glu Ala His Glu Glu Ile Asn Ile Thr Phe Thr Leu Pro
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aca gcg tgg agc tca gat gac tgc gcc ctc cac ggt cac tgt gag cag
                                                                      293
Thr Ala Trp Ser Ser Asp Asp Cys Ala Leu His Gly His Cys Glu Gln
                                -25
gtg gta ttc aca gcc tgc atg acc ctc acg gcc agc cct ggg gtg ttc
                                                                      341
Val Val Phe Thr Ala Cys Met Thr Leu Thr Ala Ser Pro Gly Val Phe
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                            -10
ccg tca ctg tac agc cac cgc act gtg ttc ctg aca cgt aca gca acg
                                                                      389
Pro Ser Leu Tyr Ser His Arg Thr Val Phe Leu Thr Arg Thr Ala Thr
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                                        10
cca cgc tct ggt aca aga tct tca caa ctg cca gag atg cca aca caa
                                                                      437
Pro Arg Ser Gly Thr Arg Ser Ser Gln Leu Pro Glu Met Pro Thr Gln
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aat acg ccc aaa att aca atc ctt tct ggt gtt ata agg ggg cca ttg
                                                                      485
Asn Thr Pro Lys Ile Thr Ile Leu Ser Gly Val Ile Arg Gly Pro Leu
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Glu Lys Ser Ile Met Leu
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                                                                      593
tggtgataac aatgttttgc tatgctgtta tcaagggcag acctagcaaa ttgcgtcaga
                                                                      653
gcaatcctga attttgtccc gagaaggtgg ctttggctga agcctaattc cacagctcct
                                                                      713
tgttttttga gagagactga gagaaccata atccttgcct gctgaaccca gcctgggcct
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                                                                      833
gtgcctgtaa ctgatttgta catatttata aaaatctatt cagaaattgg tccaataatg
                                                                      893
cacgtgcttt gccctgggta cagccagagc ccttcaaccc caccttggac ttgaggacct
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1013

1133

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ttcttgtttc agcccaatat gtagagaaca tttgaaacag tctgcacctt tgatacggta

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                                          -10
                                                                   96
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Gln Arg Pro Glu Ser Gln Glu Gly Leu Leu Pro Gly Arg Leu Val Val
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                                                                  144
Met Glu Arg Arg Val Lys Asn Asp Leu Met Ser Phe Leu Ser Thr Val
           15
                              20
ttg ttg agt ttt cac tct tct aat gca agg gtc tca cac tgt gaa cca
                                                                  192
Leu Leu Ser Phe His Ser Ser Asn Ala Arg Val Ser His Cys Glu Pro
                          35
ctt agg atg tgatcacttt caggtggcca ggaatgttga atgtctttgg
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Leu Arg Met
   45
ctcagttcat ttaaaaaaga tatctatttg aaagttctca rarttgtaca tatgtttcac
                                                                  301
agtacaggat ctgtacataa aagtttcttt cctaaaccat tcaccaagag ccaatatcta
                                                                  361
ggcattttct tggtagcaca aattttctta ttgcttaraa aattgtcctc cttgttattt
                                                                  421
                                                                  481
ctgtttgtaa racttaagtg agttaggtct ttaaggaaag caacgctcct ctgaaatgct
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ttgtatgtaa acatttcttg taggcatcac catgaacaaa gatatatttt ctatttattt
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                                          Met Ile Xaa Leu Arg Asp
aca get gee tee etc ege ett gag aga gae aca agg eag ttg eea etg
                                                                      104
Thr Ala Ala Ser Leu Arg Leu Glu Arg Asp Thr Arg Gln Leu Pro Leu
                        -20
ctc acc agt gcc ctg cac gga ctg cag cag cac cca gcc ttc tct
                                                                      152
Leu Thr Ser Ala Leu His Gly Leu Gln Gln His Pro Ala Phe Ser
                    -5
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                                                                      200
Gly Val Ala Arg Leu Ala Lys Arg Trp Val Arg Ala Gln Leu Leu Gly
            10
                                15
gag ggt ttc gct gat gag agc ctg gat ctg gtg gcc gct gcc ctt ttc
                                                                      248
Glu Gly Phe Ala Asp Glu Ser Leu Asp Leu Val Ala Ala Ala Leu Phe
                            30
ctg cac cct gag ccc ttc acc cct ccg agt tcc ccc cag gtt ggc ttc
                                                                      296
Leu His Pro Glu Pro Phe Thr Pro Pro Ser Ser Pro Gln Val Gly Phe
                        45
ctt cga ttc ctt ttc ttg gta tca acg ttt gat tgg aag aac aac ccc
                                                                      344
Leu Arg Phe Leu Phe Leu Val Ser Thr Phe Asp Trp Lys Asn Asn Pro
55
                   60
                                        65
ctc ttt gtc aac ctc aat aat gag ctc act gtg gag gag cag gtg gar
                                                                      392
Leu Phe Val Asn Leu Asn Asn Glu Leu Thr Val Glu Glu Gln Val Glu
                75
                                    80
atc ege agt gge tte etg gea get egg gea eag etc eee gte atg gte
                                                                      440
Ile Arg Ser Gly Phe Leu Ala Ala Arg Ala Gln Leu Pro Val Met Val
            90
                                95
att gtt acc ccc caa rac cgc aaa aac tct gtg tgg aca cag gat gga
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Ile Val Thr Pro Gln Xaa Arg Lys Asn Ser Val Trp Thr Gln Asp Gly
                           110
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ccc tca gcc car atc ctg cag cag ctt gtg gtc ctg gca gct gaa scc
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Pro Ser Ala Gln Ile Leu Gln Gln Leu Val Val Leu Ala Ala Glu Xaa
                        125
ctg ccc atg tta rar aas cag ctc atg gat ccc cgg gga cct ggg gac
                                                                      584
Leu Pro Met Leu Xaa Xaa Gln Leu Met Asp Pro Arg Gly Pro Gly Asp
                   140
                                       145
atc agg aca gkg ttc cgg ccg ccc ttg gac att tac gac gtg ctg att
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Ile Arg Thr Xaa Phe Arg Pro Pro Leu Asp Ile Tyr Asp Val Leu Ile
                155
                                    160
ege etg tet eet ege eat ate eeg egg eac ege eag get gtg gae ter
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Arg Leu Ser Pro Arg His Ile Pro Arg His Arg Gln Ala Val Asp Ser
                                175
            170
cca gct gcc tcc ttc tgc cgg ggc ctg ctc agc cag ccg ggg ccc tca
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Pro Ala Ala Ser Phe Cys Arg Gly Leu Leu Ser Gln Pro Gly Pro Ser
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		185					190					195					
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Ser	Leu	Met	Pro	Val	Leu	Gly	Xaa	Asp	Pro	Pro	Gln	Leu	Tyr	Leu	Thr		
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215	ьeu	naa	Gru	Ala	220	GIY	Asp	ьеи	Ala	ьеи 225	Pne	Phe	Tyr	Asp			
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His	Gly	Gly	Glu	Val	Ile	Glv	Val	Leu	Tro	Lvs	Pro	Thr	Ser	Phe	Gln		6/2
		-		235		2			240	j =				245	0111		
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Arg	Gry	265	Giu	ьeu	vaı	Met	270	PIO	ASII	vaı	GIU	A1a 275	TTE	Leu	GIU		
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Ser	Glu	Arg	Trp	Thr	Val												
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cttc	ctqc	ta c	caga	acct	a ta	ccta	gact	tac	cato	aca	ttca	ctac	ag s	atca	.ggcct		1484
ttag	atgg	ga c	ccaq	cgaa	a at	ataa	ccct	tct	gagt	cac.	atica	ccga	ca d	taao	cagtg	r	1544
gaaa	999 <u>9</u>	ct a	tatg	tgta	t ga	atag	acca	cat	tgaa	gga	gcaa	aaaa	aa a	aamo	ch		1601
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Met Gly Gly Ile Trp Asn Ala Leu Ser Met Ser Ser Phe Ser
-15
-10
ttt cat tca tcc tcc tgc tca gca ctg tca gcc aag agc tta ctc agc
158

ttt cat tca tcc tcc tgc tca gca ctg tca gcc aag agc tta ctc agc Phe His Ser Ser Ser Cys Ser Ala Leu Ser Ala Lys Ser Leu Leu Ser

206 .

aga cac cac ata ctg cag cag ttc cta gtg aga aaa tct gtg cca cta

Arg His His Ile Leu Gln Gln Phe Leu Val Arg Lys Ser Val Pro Leu

-5

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Glu Asn Ala Ser Leu Pro Phe Pro His Leu Gly Ser Ser Leu Phe Lys
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                                                                      303
Ile Val Gly
    45
gcagcccttg ttcaggtgta cagaccctta ttctggcctc tagtgtcctt gtctgtcatg
                                                                      363
acacaccett cegeceaaat acetetgace ceaaggetgg aatggggetg gtaggarata
                                                                      423
agtttgctta ctcatartca tgtcctttct cttggcacct gcttccctgc ggtgtcctca
                                                                      483
aatggatttc tgtgtggcag tggartgatt gcatgaattt ttctgtaaca cattaacttt
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gtattattat taagggartt tgaraaagct ttgcttataa tgtcaaggca aggaggtaaa
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aactggagcc caaakaaatt cccttagggc aagattatgt tataataraa aattgaattt
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cctgaggcag tggctgccac cccttttcar atgtttagtc ctgcaaatag catctttctt
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araaagtaat cttttttaca aaactgtttt tctaggtggg tggaaagtga aactgccaca
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tccttgttgg tttagtccaa raratcattt gcaacaacag taratgtccg ggttttgttt
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                                                                      117
                                                             Met
                                                             -30
cca act ggc aag cag cta gct gac att ggc tat aag acc ttc tct acc
                                                                      165
Pro Thr Gly Lys Gln Leu Ala Asp Ile Gly Tyr Lys Thr Phe Ser Thr
                                    -20
tcc atg atg ctt ctc act gtg tat ggg ggg tac ctc tgc agt gtc cga
                                                                      213
Ser Met Met Leu Leu Thr Val Tyr Gly Gly Tyr Leu Cys Ser Val Arg
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gtc tac cac tat ttc cag tgg cgc agg gcc cag cgc cag gcc gca gaa
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Val	Tyr 5	His	Tyr	Phe	Gln	Trp 10	Arg	Arg	Ala	Glr	Arg	Gln	Ala	Ala	Glu	
			dac Xaa						aact	ggg	gggc	tttt	tc t	cctg	agcar	315
tag gcc	agcg artt	ttg tga	atgg	tttt ttat	ca a gg a	accc rgct	tgtt tttg	g ga a at	agaa cgta	agtg atar	ccc	atgg	ttt	ctct	caggac ggttct rgtaca	375 435 495 536
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	0> 1> Cl 2> 9		44													
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	l> po 2> 5:		_site 527	9												
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Thr	Ala	Ile	Leu	Ala -5	Val	Ala	Val	Gly	Phe 1	Pro	Val	Ser	Gln 5	gac Asp	Gln	161
Glu	Arg	Glu 10	Lys	Arg	Ser	Ile	Ser 15	Asp	Ser	Asp	Glu	Leu 20	Ala	tca Ser	Gly	209
Xaa	Phe 25	Val	Phe	Pro	Tyr	Pro 30	Tyr	Pro	Phe	Arg	Pro 35	Leu	Pro	cca Pro	Ile	257
Pro 40	Phe	Pro	Arg	Phe	Pro 45	Trp	Phe	Arg	Arg	Asn 50	Phe	Pro	Ile	cca Pro	Ile 55	305
Pro	Glu	Ser	Ala	Pro 60	Thr	Thr	Pro	Leu	Pro 65	Ser	Glu	Lys		acaar		354
ggaa	aagt	ca	rata	aacc	t gg	tcac	ctga	aat	tgaa	att	gago	cact	tc o	ttga	araat	414
caaa	atto	ct c	gttaa	taaa	a ra	aaaa	caaa	tgt	aatt	gaa	atag	gcaca	ica c	gcatt aaacc	ctcta	474 529

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                                                                      59
aag aaa gtt ctc ctc ctg atc aca gcc atc ttg gca gtg gct gtt ggt
                                                                      107
Lys Lys Val Leu Leu Leu Ile Thr Ala Ile Leu Ala Val Ala Val Gly
                        -10
ttc cca gtc tct caa gac cak gaa cga gaa aaa aga agt atc agt gac
                                                                      155
Phe Pro Val Ser Gln Asp Xaa Glu Arg Glu Lys Arg Ser Ile Ser Asp
                5
                                    10
age gat gaa tta get tea ggg ttt ttt gtg tte eet tae eea tat eea
                                                                      203
Ser Asp Glu Leu Ala Ser Gly Phe Phe Val Phe Pro Tyr Pro Tyr Pro
                               25
ttt cgc cca ctt cca cca att cca ttt cca aga ttt cca tgg ttt aga
                                                                      251
Phe Arg Pro Leu Pro Pro Ile Pro Phe Pro Arg Phe Pro Trp Phe Arg
        35
                            40
cgt aat ttt cct att cca ata cct gaa tct gcc cct aca act ccc ctt
                                                                      299
Arg Asn Phe Pro Ile Pro Ile Pro Glu Ser Ala Pro Thr Thr Pro Leu
                       55
ccg agc gaa aag taaacaagaa ggaaaagtca cgataaacct ggtcacctga
                                                                      351
Pro Ser Glu Lys
65
aattgaaatt gagccacttc cttgargaat caaaattcct gttaataaaa gaaaaacaaa
                                                                     411
tgtaattgaa atagcacaca gcattctcta gtcaatatct ttagtgatct tctttaataa
                                                                     471
acatgaaagc aaaaaaaaa aa
                                                                     493
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seg ELSLLPSSLWVLA/TS

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-25	
tgc agc tac gct acc agg aga tct cca agc gaa ctc agc ctc ctc cca Cys Ser Tyr Ala Thr Arg Arg Ser Pro Ser Glu Leu Ser Leu Leu Pro -20 -15 -10	161
age tee etg tgg gte eta gee aca age tet eea aca att act att gea	209
Ser Ser Leu Trp Val Leu Ala Thr Ser Ser Pro Thr Ile Thr Ile Ala -5	
ctc gcg atg gcc gcc ggg aat ctg tgc ccc ctt cca tca tca tkt cgt	257
Leu Ala Met Ala Ala Gly Asn Leu Cys Pro Leu Pro Ser Ser Xaa Arg	
10 15 20 25	
crc aaa agg cgc tgg tgt cag gca asc car caa ara gct ctg ctg	302
Xaa Lys Arg Arg Trp Cys Gln Ala Xaa Gln Gln Xaa Ala Leu Leu	
30 35 40	
tagctgccac tgaaaaraag geggtgactc cagctcctcc cataaagagg tgggagctgt	362
cctcggacca gccttacctg tgacactgca ccctcacggc cacccgacta ctttgcctcc	422
ttggatttcc tccagggaga atgtgaccta atttatgaca aatacgtara gctcaggtat	482
cacttctagt tttactttaa aaaataaaaa aatagagac	521
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	120
	175
Met Val Pro Trp Pro	1,5
·	
-55	222
	223
Arg Gly Lys Val Lys Thr Ala Pro Ile Pro Ile Ser Arg Phe Pro Phe	
-50 -45 -40	
3	27Ì
Leu Pro Thr His Asp Pro Pro Thr Pro Ala His Trp Ser Pro Ala Ser	
-35 -30 -25 -20	
	319
His Gln Gln Phe Lys His Xaa Ser Pro Leu Leu Thr Leu Ala Leu Leu	
-15 -10 -5	
	367
Gly Gln Cys Ser Leu Phe Xaa Asn Leu Arg Lys Lys Leu Ala Gly Gln	
1 5 10	
aaa gca aaa aaa tta cct tcc ttc tcc agc ctg ccc ctg aca ctc tgg	415

Lys Ala Lys Lys Leu Pro Ser Phe Ser Ser Leu Pro	Leu Thr Leu Trp
cca tta act cct caa ttt gct gag ctc act aca gtg Pro Leu Thr Pro Gln Phe Ala Glu Leu Thr Thr Val 30 35 40	
ttg agg tgg tcc ggg acc cta ggt tgg ggt cca gtt Leu Arg Trp Ser Gly Thr Leu Gly Trp Gly Pro Val	ccc agc tgg gtt 51: Pro Ser Trp Val
caa ttt ttt tta ggg tgaatggagg garagttggg gactg Gln Phe Phe Leu Gly 65	gaaaas cottcaaara 566
caatgttatt acagcaktct ccccttatcc aaaktttcct ttt tatggtcaac cgcttggaaa atakttgaac acagtacaat aan ktggtggctc atgcctgtaa taatcccagg actttgtgar acc tgaacccagg aktttgarac cascctgggc aacatrgtra gad aaaaa	fatatttt gaggetggga 686 aaktttg aaggateact 746
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atgcattgca tagttgatca agtcactctc tggcctaaaa cct	
Ccctcaggat aaagtotgga cccctcagc atg gct tgt gag Met Ala Cys Glu -30	g act cat ggt gtc 233 Thr His Gly Val -25
ctt gtc cct gct cac ctc tct ggt ctc atc act tgc	
Leu Val Pro Ala His Leu Ser Gly Leu Ile Thr Cys -20 -15	Leu Leu Ala Phe -10
tgg gtc cca gcc tcc tgt atc cag aga tgc agt ggc Trp Val Pro Ala Ser Cys Ile Gln Arg Cys Ser Gly -5 5	
ctc tgattcctcc tttcttttgg tcacagagaa agggtacttt	
tctcaactta gacttgactt cctccaagga gctttggcta tac	
accetggeat actacacara teactetggg eteacttgee tge	
agtaaactgt aagctccttg agggcaagga ttgtgttgga att	
tggcttggtg cctggcacct aaaaagcact caataaatgt ttg	tttaatg aaaaaaaaaa 622 625

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                                                                      120
ttttgttctc tgctatgctc aggacccaga tcaaaggagc tcagtaacta tttacaggcg
                                                                      180
tacatcatat gtggaggaca cttatgctgt g atg gcc cca cac aca gct tcc
                                                                      232
                                   Met Ala Pro His Thr Ala Ser
                                        -35
ttt ggg gtc tgt ccc ctg ctc tcc gtt acc cgc gtg gta gcc act gag
                                                                      280
Phe Gly Val Cys Pro Leu Leu Ser Val Thr Arg Val Val Ala Thr Glu
                -25
                                    -20
cac tgg ctc ttc ctg gct tca ctc tct ggc atc aaa act tat cag tcc
                                                                      328
His Trp Leu Phe Leu Ala Ser Leu Ser Gly Ile Lys Thr Tyr Gln Ser
            -10
                                -5
tac atc tca gtc ttt tgc aag gtg aca ctt atc tgattaccta attcacacra
                                                                      381
Tyr Ile Ser Val Phe Cys Lys Val Thr Leu Ile
                       10
aggtgttaat ggtggtaatg gcataktatt tattacccca ggggacccak aacggtggta
                                                                      441
tcaaaacata tcattcccca gtggtttaaa actctggtag ctttccargg aatccaaagt
                                                                      501
ggaatccagt ctccttagct gawttcacag ggccccgtct gcacaacttg gcttctgtcg
                                                                      561
getteectan ecctgaette ceaageetta gteateacce teteteceae ecagggetea
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gcacagtacc tggaacagtc aagccctcaa taaatgttta ctgagtgcat yaaaaaaaa
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<222> 777..782

<221> polyA_site

<222> 801..812

<211> 813

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gca gac tca act gag aag tca gcc tct gcg gca ggc acc agg aat ctg Ala Asp Ser Thr Glu Lys Ser Ala Ser Ala Ala Gly Thr Arg Asn Leu -45 -40 -35	154
cct ttt cag ttc tgt ctc cgg cag gct ttg agg atg aag gct gcg ggc Pro Phe Gln Phe Cys Leu Arg Gln Ala Leu Arg Met Lys Ala Ala Gly -30 -25 -20 -15	202
att ctg acc ctc att ggc tgc ctg gtc aca ggc gtc gag tcc aaa atc Ile Leu Thr Leu Ile Gly Cys Leu Val Thr Gly Val Glu Ser Lys Ile -10 -5	250
tac act cgt tgc aaa ctg gca aaa ata ttc tcg agg gct ggc ctg gac Tyr Thr Arg Cys Lys Leu Ala Lys Ile Phe Ser Arg Ala Gly Leu Asp 5 10	298
aat cyg agg ggc ttc agc ctt gga aac tgg atc tgc atg gcg tat tat Asn Xaa Arg Gly Phe Ser Leu Gly Asn Trp Ile Cys Met Ala Tyr Tyr 20 25 30	346
gag agc ggc tac aac acc aca gcc car acg gtc ctg gat gac ggc agc Glu Ser Gly Tyr Asn Thr Thr Ala Gln Thr Val Leu Asp Asp Gly Ser 35 40 45 50	394
atc gac tay ggc atc ttc caa atc aac agc ttc gcg tgg tgc aga cgc Ile Asp Tyr Gly Ile Phe Gln Ile Asn Ser Phe Ala Trp Cys Arg Arg 55 60 65	442
gga aag ctg aag gag aac aac cac tgc cay gtc gcc tgc tca gcc ttg Gly Lys Leu Lys Glu Asn Asn His Cys His Val Ala Cys Ser Ala Leu 70 75 80	490
rtc act gat gac ctc aca gat gca att atc tgt gcc arg aaa att gtt Xaa Thr Asp Asp Leu Thr Asp Ala Ile Ile Cys Ala Xaa Lys Ile Val 85 90 95	538
aaa gag aca caa gga atg aac tat tgg caa ggc tgg aag aaa cay tgt Lys Glu Thr Gln Gly Met Asn Tyr Trp Gln Gly Trp Lys Lys His Cys 100 105 110	586
gag ggg aga gac ctg tcc gas tgg aaa aaa ggc tgt gag gtt tcc Glu Gly Arg Asp Leu Ser Xaa Trp Lys Lys Gly Cys Glu Val Ser 115 120 125	631
taaactggaa ctggacccag gatgctttgc ascaacgccc tagggtttgc agtgaatgtc	691
caaatgcctg tgtcatcttg tcccgtttcc tcccaatatt ccttctcaaa cttggagagg	751
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<210> 294

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<210> 295

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<222> 154..360

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<222> 1017..1022

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Accepting a gegacidaga accasagit accasa accident togaacited gagacited (17)				cacto	ggaat	ca ao	ggaag	aaact	gat	tgact	ttc	agaa	agato	gaa (ggtaa	agtaga	60
Ctggaaccaa cgggcacagt tggcaacac atc atg aca cca cct gtt ccc 174																	120
## Met Thr Ser Gln Pro Val Pro																	174
aat gag acc atc ata gtg ctc cca tca ast gtc atc acc acc cas as gtc atc acc acc acc acc acc acc acc acc a	0055	,		-555		,	٠		-	Met	t Thi	c Sei	c Glı	n Pro	o Vai	l Pro	
Asn Glu Thr Ile Ile Val Leu Pro Ser Asn Val Ile Asn Phe Ser Gln -60																	
Asn Glu Thr Ile Ile Val Leu Pro Ser Asn Val Ile Asn Phe Ser Gln -60	aat	gag	acc	atc	ata	ata	ctc	cca	tca	aat	qtc	atc	aac	ttc	tcc	caa	222
The column The	Asn	Glu	Thr	Tle	Tle	Val	Leu	Pro	Ser	Asn	Val	Ile	Asn	Phe	Ser	Gln	
gca gag aaa ccc gaa ccc acc acc cag gg cag gat agc ctg aag aaa 270 Ala Glu Lys Pro Glu Pro Thr Asn Gln dly Gln Asp Ser Leu Lys Lys -45 -40 -35 -35 -31 -36 -36 -36 -36 -31 -36 -36 -36 -31 -36	11011																
Ala Glu Lys Pro Glu Pro Thr Asn Gln Gly Gln Asp Ser Leu Lys Lys -45 cat cta cac gca gar rtc aaa gtt att ggg act atc cag atc ttg tgt 318 His Leu His Ala Glu Xaa Lys Val Ile Gly Thr Ile Gln Ile Leu Cys -30 ggc atg atg gta ttg agc ttg ggg atc atc ttg gct tcc ttc 366 Gly Met Met Val Leu Ser Leu Gly Ile Ile Leu Ala Ser Ala Ser Phe -10 cca att tt acc caa gtg act tct aca ctg ttg aac tct gct tac Ser Phe -10 scr Pro Asn Phe Thr Gln Val Thr Ser Thr Leu Leu Asn Ser Ala Tyr 5 cca ttc ata gga ccc ttt ttt tt atc atc tct ggc tct cta acc acc gct acc aca acc acc acc acc acc acc acc a	aca	aaa		ccc	gaa	ccc	acc	aac	caq	qqq	caq	qat	agc	ctg	aag	aaa	270
-45																	
cat cac gar rtc aaa gtt att gg atc ctg tgt tgt tac cps rac			-1-							1					-	-	
His Leu His Ala Glu Xaa Lys Val Ile Gly Thr Ile Gln Ile Leu Cys -30 -30 -25 -30 -25 -30 -25 -30 -25 -30 -30 -35 -36 -30 -36 -36 -30 -36 -36 -36 -36 -36 -36 -36 -36 -36 -36	cat	_	cac	\qca	gar	rtc	aaa	qtt	att	ggg	act	atc	cag	atc	ttg	tgt	318
-30	His	Leu	His	Ala	Glu	Xaa	Lys	Val	Ile	Gly	Thr	Ile	Gln	Ile	Leu	Cys	
ggc atg atg atg gta ttg agc ttg ggg atc atg stt ttg gca tct gct tcc tcc stc stc stc stc stc stc stc stc stc							•			-							
Gly Met Met Val Leu Ser Leu Gly Ile Ile Leu Ala Ser Ala Ser Phe 1		atq	atq	qta	tta	agc	ttq	qqq	atc	att	ttq	qca	tct	gct	tcc	ttc	366
1	Gly	Met	Met	val	Leu	Ser	Leu	Gly	Ile	Ile	Leu	Āla	Ser	Āla	Ser	Phe	
Ser Pro Asn Phe Thr Gln Val Thr Ser Thr Leu Leu Asn Ser Ala Tyr 15	•							-									
Ser Pro Asn Phe Thr Gln Val Thr Ser Thr Leu Leu Asn Ser Ala Tyr 15	tct	cca	aat	ttt	acc	caa	gtg	act	tct	aca	ctg	ttg	aac	tct	gct	tac	414
S																	
Pro Phe Ile Gly Pro Phe Phe Phe Phe Ile Ile Ser Gly Ser Leu Ser Ile 20																	
Pro Phe Ile Gly Pro Phe Phe Phe Phe Ile Ile Ser Gly Ser Leu Ser Ile 20	cca	ttc	ata	gga	ccc	ttt	ttt	ttt	atc	atc	tct	ggc	tct	cta	tca	atc	462
gcc aca aaa aaa agg tta acc acc cac ctt ttg gtg cat acc acc ctg gtt 10	Pro	Phe	Ile	Gly	Pro	Phe	Phe	Phe	Ile	Ile	Ser	Gly	Ser	Leu	Ser	Ile	
Ala Thr Lys Lys Arg Leu Thr Asn Leu Leu Val His Thr Thr Leu Val 35																	
Ala Thr Lys Lys Arg Leu Thr Asn Leu Leu Val His Thr Thr Leu Val 35	gcc	aca	aaa	aaa	agg	tta	acc	aac	ctt	ttg	gtg	cat	acc	acc	ctg	gtt	510
35	Ala	Thr	Lys	Lys	Arg	Leu	Thr	Asn	Leu	Leu	Val	His	Thr	Thr	Leu	Val	
Ser The Leu Ser Ala Leu Ser Ala Leu Val Gly Phe The Xaa Leu Ser Color Colo			_	-	_												
S																	558
CCL gtc aaa cag gcc acc tta aat cct gcc tca ctg cak tgt gag ttg 606	Gly	Ser	Ile	Leu	Ser	Ala	Leu	Ser	Ala	Leu	Val	Gly	Phe	Ile	Xaa	Leu	
Ser Val Lys Gln Ala Thr Leu Asn Fro Ala Ser Leu Xaa Cys Glu Leu 70 75 80 80 80 90 95 95 95 95 95 95 95 95 95 95 95 95 95																	
gmc aaa aat aat aat acc aca ara akt tat gtt yct tac ttt tat cat 654 Xaa Lys Asn Asn Ile Pro Thr Xaa Xaa Tyr Val Xaa Tyr Phe Tyr His 85 gat tca ctt tat acc acg gac kgc tat aca gcc aaa gcc akt ctg gct 702 Asp Ser Leu Tyr Thr Thr Asp Xaa Tyr Thr Ala Lys Ala Xaa Leu Ala 100 gga act ctc tct ctg atg ctg att tgc act ctg ctg gaa ttc tgc cwa 750 Gly Thr Leu Ser Leu Met Leu Ile Cys Thr Leu Leu Glu Phe Cys Xaa 115 sct gtg ctc act gct gtg ctg cgg tgg aaa cag gct tac tct gac ttc 798 Xaa Val Leu Thr Ala Val Leu Arg Trp Lys Gln Ala Tyr Ser Asp Phe 135 cct ggg agt gta ctt ttc ctg cct cam agt tac att ggw aat tct ggm 846 Pro Gly Ser Val Leu Phe Leu Pro Xaa Ser Tyr Ile Gly Asn Ser Gly 150 atg tcc tca aaa atg acy cat gac tgt gga tat gaa gaa cta ttg act 894 Met Ser Ser Lys Met Thr His Asp Cys Gly Tyr Glu Glu Leu Leu Thr 165 tct taagaaaaaa gggagaaata ttaatcagaa agttgattt cctaaatgta agctttaaa 1007	tct	gtc	aaa	cag	gcc	acc	tta	aat	cct	gcc	tca	ctg	cak	tgt	gag	ttg	606
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Xaa Lys Asn Asn Ile Pro Thr Xaa Xaa Tyr Val Xaa Tyr Phe Tyr His gat tca ctt tat acc acg gac kgc tat aca gcc akt ctg gct 702 Asp Ser Leu Tyr Thr Thr Asp Xaa Tyr Thr Ala Lys Ala Xaa Leu Ala 100 105 105 110 1									_								
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gag tgg tcg gcg ttc ctg gag gcg rmc gat aac ttg cgt ctg atc cag Glu Trp Ser Ala Phe Leu Glu Ala Xaa Asp Asn Leu Arg Leu Ile Gln 35 . 40 45 50 gtg ccg aga agg gcc ggt tgagggatat gaggagaatg aggagtttct Val Pro Arg Arg Ala Gly 55	298 358
gag tgg tcg gcg ttc ctg gag gcg rmc gat aac ttg cgt ctg atc cag Glu Trp Ser Ala Phe Leu Glu Ala Xaa Asp Asn Leu Arg Leu Ile Gln 35 . 40 45 50 gtg ccg aga agg gcc ggt tgagggatat gaggagaatg aggagtttct Val Pro Arg Arg Ala Gly 55 gaggaccatg caccacctgc tgctggaggt ggamstgaka gagggcaccc tgcagtgccc ggaatctgga cgtatgttcc ccatcagccg cgggatcccc aacatgctgc tgagtgaaga	358 418
gag tgg tcg gcg ttc ctg gag gcg rmc gat aac ttg cgt ctg atc cag Glu Trp Ser Ala Phe Leu Glu Ala Xaa Asp Asn Leu Arg Leu Ile Gln 35 . 40 45 50 gtg ccg aga agg gcc ggt tgagggatat gaggagaatg aggagttct Val Pro Arg Arg Ala Gly 55 gaggaccatg caccacctgc tgctggaggt ggamstgaka gagggcaccc tgcagtgccc ggaatctgga cgtatgttcc ccatcagccg cgggatcccc aacatgctgc tgagtgaaga ggaaactgag agttgattgt gccaggcgcc agttttctt gttatgactg tgtatttttg	358 418 478
gag tgg tcg gcg ttc ctg gag gcg rmc gat aac ttg cgt ctg atc cag Glu Trp Ser Ala Phe Leu Glu Ala Xaa Asp Asn Leu Arg Leu Ile Gln 35 . 40 45 50 gtg ccg aga agg gcc ggt tgagggatat gaggagaatg aggagttct Val Pro Arg Arg Ala Gly 55 gaggaccatg caccacctgc tgctggaggt ggamstgaka gagggcaccc tgcagtgccc ggaatctgga cgtatgttcc ccatcagccg cgggatcccc aacatgctgc tgagtgaaga ggaaactgag agttgattgt gccaggcgcc agtttttctt gttatgactg tgtatttttg ttgatctata ccctgtttcc gaattctgcc gtgtgtatcc ccaacccttg acccaatgac	358 418
gag tgg tcg gcg ttc ctg gag gcg rmc gat aac ttg cgt ctg atc cag Glu Trp Ser Ala Phe Leu Glu Ala Xaa Asp Asn Leu Arg Leu Ile Gln 35 . 40 45 50 gtg ccg aga agg gcc ggt tgagggatat gaggagaatg aggagttct Val Pro Arg Arg Ala Gly 55 gaggaccatg caccacctgc tgctggaggt ggamstgaka gagggcaccc tgcagtgccc ggaatctgga cgtatgttcc ccatcagccg cgggatcccc aacatgctgc tgagtgaaga ggaaactgag agttgattgt gccaggcgcc agttttctt gttatgactg tgtatttttg	358 418 478 538

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                                   Met Lys Ser Ala Lys Leu Gly
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ttt ctt cta aga ttc ttc atc ttc tgc tca ttg aat acc ctg tta ttg
                                                                      100
Phe Leu Leu Arg Phe Phe Ile Phe Cys Ser Leu Asn Thr Leu Leu Leu
        -15
                            -10
                                         -5
ggt ggt gtt aat aaa att gcg gag aag ata tgt gga gac ctc aaa gat
                                                                      148
Gly Gly Val Asn Lys Ile Ala Glu Lys Ile Cys Gly Asp Leu Lys Asp
                                        10
ccc tgc aaa ttg gac atg aat ttt gga agc tgc tat gaa gtt cac ttt
                                                                      196
Pro Cys Lys Leu Asp Met Asn Phe Gly Ser Cys Tyr Glu Val His Phe
                20
aga tat ttc tac aac aga acc tcc aaa aga tgt gaa act ttt gtc ttc
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Arg Tyr Phe Tyr Asn Arg Thr Ser Lys Arg Cys Glu Thr Phe Val Phe
            35
tcc agc tgt aat ggc aac ctt aac aac ttc aag ctt aaa ata gaa cgt
                                                                      292
Ser Ser Cys Asn Gly Asn Leu Asn Asn Phe Lys Leu Lys Ile Glu Arg
        50
                            55
gaa gta kcc tgt gtt gca aaa tac aaa cca ccg agg tgagaggatg
                                                                      338
Glu Val Xaa Cys Val Ala Lys Tyr Lys Pro Pro Arg
                        70
tgaactcatg aagttgtctg ctgcaccatc cgaaataaag acacaagaaa attcaractg
                                                                      398
atttwgaaat ctttgttwta tttccmymak ggcgwktaag cttccatatg tttgctattt
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ageggeaaga tegeatetee eggete atg gge gae tat etg etg ege ggt tae	173
Met Gly Asp Tyr Leu Leu Arg Gly Tyr	
-75 -70	
cgc atg ctg ggc gag acg tgt gcg gac tgc ggg acg atc ctc cta caa	221
Arg Met Leu Gly Glu Thr Cys Ala Asp Cys Gly Thr Ile Leu Leu Gln	
-65 -60 -55	
gac aaa cag cgg aaa atc tac tgc gtg gct tgt cag gaa ctc gac tca	269
Asp Lys Gln Arg Lys Ile Tyr Cys Val Ala Cys Gln Glu Leu Asp Ser	
-50 -45 -40	217
gac gtg gat aaa gat aat coo got ctg aat goo cag got goo ctc too	317
Asp Val Asp Lys Asp Asn Pro Ala Leu Asn Ala Gln Ala Ala Leu Ser -35 -30 -25 -20	
caa gct cgg gag cac cag ctg gcc tca gcc tca gag ctc ccc ctg ggc	365
Gln Ala Arg Glu His Gln Leu Ala Ser Ala Ser Glu Leu Pro Leu Gly	303
-15 -10 -5	
tot cga cot gcg coc caa coc cca gta cot cgt ccg gag cac tgt gag	413
Ser Arg Pro Ala Pro Gln Pro Pro Val Pro Arg Pro Glu His Cys Glu	
1 5 10	
gga gct gca gca gga ctc aag gca gcc cag ggg cca cct gct cct gct	461
Gly Ala Ala Ala Gly Leu Lys Ala Ala Gln Gly Pro Pro Ala Pro Ala	
15 20 _. 25	
gtg cct cca aat aca rat gtc atg gcc tgc aca cag aca gcc ctc ttg	509
Val Pro Pro Asn Thr Xaa Val Met Ala Cys Thr Gln Thr Ala Leu Leu	
30 35 40 45	
caa aag ctg acc tgg gcc tct gct gaa ctg ggc tct anc acc tcc cyg	557
Gln Lys Leu Thr Trp Ala Ser Ala Glu Leu Gly Ser Xaa Thr Ser Xaa 50 55 60	
	605
gga aaa mta gca tcc agc tgt gtg gcc tta tcc gcg cat gtg cgg agg Gly Lys Xaa Ala Ser Ser Cys Val Ala Leu Ser Ala His Val Arg Arg	605
65 70 75	
ccc tgc gca gcc tgc agc agc tac agc act aag aga agc ccc	647
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cgt ctt cag gaa gcc aga cag att caa gta ttg aag atg ctt cca agg Arg Leu Gln Glu Ala Arg Gln Ile Gln Val Leu Lys Met Leu Pro Arg -5 1 5 10	339
gaa aaa tta aga aga aga gaa gag aga aaa caa ata aat ggg aaa aaa Glu Lys Leu Arg Arg Arg Glu Glu Arg Lys Gln Ile Asn Gly Lys Lys 15 20 25	387
raa agg aca aaa tat gaa aca cca aga aaa rga raa gga aaa aaa gga Xaa Arg Thr Lys Tyr Glu Thr Pro Arg Lys Xaa Xaa Gly Lys Lys Gly 30 35 40	435
gga aac mac cmc wtw tkt cmc ctt tcc aar agg gac tgaaactggg Gly Asn Xaa Xaa Xaa Xaa Leu Ser Lys Arg Asp 45 50 55	481
ctgacccttt tgatttccaa vctcascgtt ttggtgtaag gcggccaaar aaggatgcgg	541
ascccagcac tgtgaagcct acaaaaacat tgatgcgctg gcttggggat ttgaatttga	601
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aga gtg agc tcg gtg gga gcg aat ktc cta tgc ctg ggg atg gcc ctg Arg Val Ser Ser Val Gly Ala Asn Xaa Leu Cys Leu Gly Met Ala Leu -20 -15 -10	157

					_	_		ccg Pro								205
acc					atg			gtg Val 20	aar					gag		253
			gar					cac His					atc			301
		tcg			_	_	tgc	gct Ala		_		tta				349
	agt					ctt		gat Asp			gaa					397
ggt					ctt			ggc Gly								445
				agc				ttt Phe 100	gtc					aac		493
			aca					caa Gln					acg			541
		stc					gcc	atc Ile				atg				589
	gtc	_		_		cac	_	aaa Lys	-		att	_				637
gtg					tat			tgg Trp		ttg					aaa	685
				gga	_		_	aat Asn 180	ctg					ttt		733
	_		gga					atc Ile			_	_	tgc			781
		ctc					gac	tca Ser				gtg				829
	aac					cct		aag Lys			aac				gga Gly 235	877
act					gag			aaa Lys		gtc					act	925
				gag				atg Met 260	aaa					tgg		973
			tct					aca					aag			1021
		ata					acc	ata Ile				ctc				1069
	gaa					agt		cct Pro			ctg					1117
att					aag			ctg Leu		cct					cat	1165

320 325 330	
	1213
ctt taaagttgcc taaaactacc attccgaaat tattgaagag atcatagata Leu	1266
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Met Val Cys Leu Phe Phe Arg Leu Ile Phe Ser Glu His Leu Pro Ile	
-10 -5 1 5	
ata ggc act gtc act tct cac aaa act ggg aca cta act gtt tat cca	152
Ile Gly Thr Val Thr Ser His Lys Thr Gly Thr Leu Thr Val Tyr Pro	
10 15 20	
aca tot got ggc taaataaaga catgatotto acottttggg attgttaatt	204
Thr Ser Ala Gly 25	
taaaatggtt ccataagagc aatgcaaaga cagagatatt tggcagcact gcagctggtg	264
atttatatgg ctcttcacaa ggtgttattt tggggtatca aggtatggat gcttaaatca	324
gctgcaggaa gtaagaaaga agaaaaaagg agtgataaag ataaaaaaaa	384
gtccttccac caaaacccat taatttccat atcatcatct gcataararg gaaaattcct	444
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                                                                     120
ggcattccag gacctccgma atgatgctcc agtcccttac aagcgcttcc tggatgaggg
                                                                     180
tggc atg gtg ctg acc acc ctc ccc ttg ccc tct gcc aac agc cct gtg
                                                                     229
     Met Val Leu Thr Thr Leu Pro Leu Pro Ser Ala Asn Ser Pro Val
             -35
                                                                     277
aac atq ccc acc act qqc ccc aac aqc ctq aqt tat gct agc tct gcc
Asn Met Pro Thr Thr Gly Pro Asn Ser Leu Ser Tyr Ala Ser Ser Ala
 - -20
                            -15
ctg tcc ccc tgt ctg acc gct cca aag tcc ccc cga ctt gct atg atg
                                                                     325
Leu Ser Pro Cys Leu Thr Ala Pro Lys Ser Pro Arg Leu Ala Met Met
                       1
                                       5
                                                                     374
cct gac aac taaatatcct tatccaaatc aataaarwra raatcctccc
Pro Asp Asn
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gaattttatc tagaaaagaa gactaagcag cttttgttct tctgtgaccc agttgctggc
ccaagacatg gaca atg acc ccc tgg tgt ttg gcg tgt ctg ggg agg agg
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Met Thr Pro Trp Cys Leu Ala Cys Leu Gly Arg Arg -20 278 cct ctc gct tct ttg cag tgg agc ctg aca ctg gcg tgg tgt ggc tcc Pro Leu Ala Ser Leu Gln Trp Ser Leu Thr Leu Ala Trp Cys Gly Ser -10 - 5 ggc agc cac tgg aca gag aga cca akt cag akt tca ccg tgg akt tct 326 Gly Ser His Trp Thr Glu Arg Pro Xaa Gln Xaa Ser Pro Trp Xaa Ser 10 15 377 ctg tca gcg acc acc agg ggg tgatcacacg gaaggtgaac atccaggtcg Leu Ser Ala Thr Thr Arg Gly 20 25 437 gggatgtgaa tgacaacgcg cccacatttc acaatcagcc ctacagcgtc cgcatccctg 497 araatacacc agtggggacg cccatcttca tcgtgaatgc cacagacccc gacttggggg cagggggcag cgtcctctac tccttccagc cccctccca attcttcgcc attgacagcg 557 cccgcggtat cktcacagtg atccgggagc tggactacga taccacrcmg gcctaccagc 617 677 tcwcggtcwa cgccacagat caagacaara ccaggcctct gtccaccstg gccaacttgg ccatcatcat cacagatgtc caggacatgg accccatctt catcaacctg ccttacagca 737 ccaacatcta cgagcattct cctccgggca cgacggtgcg catcatcacc gccatagacc 797 aggataaagg acgtccccgg ggcattggct acaccatcgt ttcagggcat ctgtgtttac aagaacccaa gatctctcag gagctcagga aaaggggctt gctgtgaggc tcagggttcc catggacatt ctgagctgac cctcctcagc attggatctc ctggctcagg aactaggaac 1037 gaagettgga tgttttetee ttteetacag catetgtatt cattteetat agttgecata 1087 ataaaatgcc actaacttag tggcttaaaa accaaaaaaaa aaaaaccctt <210> 311 <211> 916 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 90..815 <221> sig_peptide <222> 90..179 <223> Von Heijne matrix score 13.1999998092651 seg LLLLSTLVIPSAA/AP <221> polyA signal <222> 883..888 <221> polyA site <222> 905..916 <400> 311 60 aaaacagtac gtgggcggcc ggaatccggg agtccggtga cccgggctgt ggtctagcat aaaggeggag ccagaagaag gggeggggt atg gga gaa gee tee eea eet gee 113 Met Gly Glu Ala Ser Pro Pro Ala -30 -25 161 ccc gca agg cgg cat ctg ctg gtc ctg ctg ctc ctc tct acc ctg Pro Ala Arg Arg His Leu Leu Val Leu Leu Leu Leu Ser Thr Leu -20 -15 -10 209 gtg atc ecc tec get gea get eet atc eat gat get gac gee caa gag Val Ile Pro Ser Ala Ala Ala Pro Ile His Asp Ala Asp Ala Gln Glu 1 257 age tee ttg ggt etc aca gge etc cag age eta etc caa gge tte age Ser Ser Leu Gly Leu Thr Gly Leu Gln Ser Leu Leu Gln Gly Phe Ser 1.5 20

cga ctt ttc ctg aaa ggt aac ctg ctt cgg ggc ata gac agc tta ttc

305

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Arg Leu Phe Leu Lys Gly Asn Leu Leu Arg Gly Ile Asp Ser Leu Phe
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            30
tot god cod atg gad ttd egg ggd ctd cot ggg aad tad dad aaa gag
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Ser Ala Pro Met Asp Phe Arg Gly Leu Pro Gly Asn Tyr His Lys Glu
        45
                            50
                                                                      401
gag aac cag gag cac cag ctg ggg aac aac acc ctc tcc agc cac ctc
Glu Asn Gln Glu His Gln Leu Gly Asn Asn Thr Leu Ser Ser His Leu
                        65
cag atc gac aag atg acc gac aac aag aca gga gag gtg ctg atc tcc
                                                                      449
Gln Ile Asp Lys Met Thr Asp Asn Lys Thr Gly Glu Val Leu Ile Ser
                    80
                                        85
                                                                      497
gag aat gtg gtg gca tcc att caa cca vcg gag ggg anc ttc gag ggt
Glu Asn Val Val Ala Ser Ile Gln Pro Xaa Glu Gly Xaa Phe Glu Gly
                95
                                    100
                                                                      545
gat ttg aag gth ccc agg atg gag gar aag gag gcc ctg gta ccc mtc
Asp Leu Lys Val Pro Arg Met Glu Glu Lys Glu Ala Leu Val Pro Xaa
          \110
                                 115
car aag gcc acg gac agc ttc cac aca gaa ctc cat ccc cgg gtg gcc
                                                                      593
Gln Lys Ala Thr Asp Ser Phe His Thr Glu Leu His Pro Arg Val Ala
                            130
ttc tgg atc att aag ctg cca cgg cgg agg tcc cac cag gat gcc ctg
                                                                      641
Phe Trp Ile Ile Lys Leu Pro Arg Arg Ser His Gln Asp Ala Leu
    140
gag ggc ggc cac tgg ctc anc gar aag cga cac cgc ctg cag gcc atc
                                                                      689
Glu Gly Gly His Trp Leu Xaa Glu Lys Arg His Arg Leu Gln Ala Ile
                    160
cgg gat gga ctc cgc aag ggg acc cac aag gac rtc cta daa rag ggg
                                                                      737
Arg Asp Gly Leu Arg Lys Gly Thr His Lys Asp Xaa Leu Xaa Xaa Gly
                175
                                     180
acc gar agc tcc tcc cac tcc agg ctg tcc ccc cga aar amm cac tta
                                                                      785
Thr Glu Ser Ser His Ser Arg Leu Ser Pro Arg Lys Xaa His Leu
                                195
                                                    200
ctg tac atc ctc arg ccc tct cgg cag ctg targggtggg gaccgggggar
                                                                      835
Leu Tyr Ile Leu Xaa Pro Ser Arg Gln Leu
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agg cgg cag aag ttg ctt ctt g Arg Arg Gln Lys Leu Leu Leu A -40			3
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agg acc ctg ctg gtt gct gcc c Arg Thr Leu Leu Val Ala Ala L -10 -5			9
tgg agg acg ttg gtg cag aga c Trp Arg Thr Leu Val Gln Arg A			7
ttr ggg gtc tac gtc atc cag g Leu Gly Val Tyr Val Ile Gln G 25			5
tgc atc cgc atg tgg cag tgc c Cys Ile Arg Met Trp Gln Cys A 40			3
gct ctc tgc ttg ttc cag gtc c Ala Leu Cys Leu Phe Gln Val P 55 60		-	1
gat ggc ttt tta cag gtc caa t Asp Gly Phe Leu Gln Val Gln T			9
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														Met	Asn	
															-60	
gca Ala	gcc Ala	atc Ile	aac Asn	acg Thr	ggc	cct Pro	gcc Ala	cct Pro	gct Ala -50	gtc Val	acc Thr	aag Lys	act Thr	gag Glu -45	act Thr	225
~~~	ata	cad	22t		ast	a++	ata	+ ~ ~		++~	~~~	2 + 4			aaa	273
														gaa Glu		213
agg	aqc	cat	qct	qac	caa	qac	agc	-	ccc	aaq	aca	qaa	qcc	ctg	ctc	321
														Leu		
ccc	tgc	aac	ctg	cac	tgc	agc	tgg	ctc	cac	agc	agc	ccc	agg	cca	gat	369
Pro	Cys -10	Asn	Leu	His	Cys	Ser -5	Trp	Leu	His	Ser	Ser 1	Pro	Arg	Pro	Asp 5	
														cac		417
Pro	His	Ser	His	Phe 10	Pro	Ser	Xaa	Arg	Arg 15	Cys	Pro	Leu	Pro	His 20	Pro	
			tac Tyr 25				tgaa	accad	ctc t	gtct	ccta	at co	cttt	ggcca	à	468
ccto	tcct	da a		atat	-t ct	cttc	-catt		rt cct	cap	toto	3000	י מסי	raacra	accata	528
_		_		_						_					ggaget	588
_			_					_	_			-			acagag	648
	_	_			-	-		a aac						_	<b>J</b> J	697
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		olyA_ 0	_sigr 775	nal												
		olyA_ 928	_site 303	•												
400																
	)> 3]													~ ~ * ~ .		60
			_		_		_					_			atcttc ccgatc	120
			_												ga gta	174
ccgc	uucc	ige (		Laac	בר ני	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,									rg Val	1/3
							•••		25					20		
cta	ctc	acc	taa	ctt	ttc	aca	cta			tta	atc	ato		gtg	tta	222
														Val		
		-15	•		_		-10	_			_	- 5				
aaa	ctg		gag	aaa	gca	cct		aac	tgg	ttc	ctc	_	ttc	att	cca	270
	_	_			_									Ile		
-	1	-		-	5		-		-	10					15	
gtc	tgg	ata	ttt	gat	act	atc	ctt	ctt	gtc	ctg	ctg	att	gtg	aaa	atg	318
														Lys		

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20
                                    25
                                                                      366
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                                                                      546
gactictaag tacatcatct ccttictatt gctgttcaac aagttaccat taaagtgttc
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tactacttcc ataaaacagg attggtgaat cacggacttc tagtcaacct acagcttaat
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ccaaagcagc actegttgcc aattagggaa tggaccgttt gggttccttt agca atg
                                                                      225
atc cct ctg ata agc cac ctt gcc gag gct gct cct cct acc tca tgg
Ile Pro Leu Ile Ser His Leu Ala Glu Ala Ala Pro Pro Thr Ser Trp
            -30
                                -25
                                                    -20
                                                                      273
age ett ata tea agt gtg etg aat gtg gge eac ete ett tit tee tet
Ser Leu Ile Ser Ser Val Leu Asn Val Gly His Leu Leu Phe Ser Ser
       -15
                           -10
                                                -5
                                                                      321
get tge agt gtt tea ete gag get ttg agt aca aga aac ate aaa geg
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                   5
atc ata ctt atg aaa taatggcttc agattttcct gtccttgatc ccagctggac
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Ile Ile Leu Met Lys
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tgctcaagaa raaatggccc ttttagaasc tgtgatggac tgtggctttg gaaattggca
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ggatgtagcc aatcaaatgt gcaccaarac caaggaggag tgtgagaagc actatatgaa
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gcatttcatc aataacccyc tgtttgcatc trscctgctg aacctgaaac aascagrgga
                                                                      616
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           Met Glu Ser Pro Gln Leu His Cys Ile Leu Asn Ser Asn
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Ser Val Ala Cys Ser Phe Ala Val Gly Ala Gly Phe Leu Ala Phe Leu
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age tge etg gee tte ete gte etg gae aca eag gag ace ege att gee
                                                                     325
Ser Cys Leu Ala Phe Leu Val Leu Asp Thr Gln Glu Thr Arg Ile Ala
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ggc acc cgc ttc aag aca gcc ttc cag ctc ctg gac ttc atc ctg gct
                                                                     373
Gly Thr Arg Phe Lys Thr Ala Phe Gln Leu Leu Asp Phe Ile Leu Ala
                           15
gtt ctc tgg gca gtt gtc tgg ttc atg ggt ttc tgc ttc ctg gcc aac
                                                                     421
Val Leu Trp Ala Val Val Trp Phe Met Gly Phe Cys Phe Leu Ala Asn
                        3.0
caa tgg cag cat tcg ccg ccc aaa gar kkc ctc ctg ggg agc agc agt
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Gln Trp Gln His Ser Pro Pro Lys Glu Xaa Leu Leu Gly Ser Ser Ser
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gcc cag gca gcc atc ggc stt cac ctt ctt ctc cat cct tgt ctg gat
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Ala Gln Ala Ala Ile Gly Xaa His Leu Leu Leu His Pro Cys Leu Asp
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                                    65
att cca rgc cta cct ggc akk cca gga cct ccg aaa tgatgctcca
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Ile Pro Xaa Leu Pro Gly Xaa Pro Gly Pro Pro Lys
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-235-

Since graph in magnetic and services of

Supplied to the process of the second of the

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Ser Glu Val Gln Phe Ser Ala Phe Cys Pro Tyr Trp Thr Ile Ala Arg
ata tta gaa cgt gtt ggt tcc gcg tgc ttc cgt ctt gag tta tgt gct
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Ile Leu Glu Arg Val Gly Ser Ala Cys Phe Arg Leu Glu Leu Cys Ala
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                        -20
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Leu Cys Leu Ser Ser Leu Thr Ala Phe Gly Thr Pro Pro Ile Gly Val
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cac att ccc tct ccc tararcacac tcccttggat ttcctcradt ggggtctgct
His Ile Pro Ser Pro
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526

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Ser Leu Thr Ser Ser Pro Val Arg Leu Leu Leu Xaa Leu Leu Leu Leu
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                                    -10
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Leu Ile Ala Leu Glu Ile Met Val Gly Gly His Ser Leu Cys Phe Asn
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ttc act ata aaa tca ttg tcc aga cct gga cag ccc tgg tgt gaa gcg
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Phe Thr Ile Lys Ser Leu Ser Arg Pro Gly Gln Pro Trp Cys Glu Ala
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cat gtc ttc ttg aat aaa aat ctt ttc ctt cag tac aac agt gac aac
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His Val Phe Leu Asn Lys Asn Leu Phe Leu Gln Tyr Asn Ser Asp Asn
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Asn Met Val Lys Pro Leu Gly Leu Leu Gly Lys Lys Val Tyr Ala Thr
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Ser Thr Trp Gly Glu Leu Thr Gln Thr Leu Gly Glu Val Gly Arg Asp
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ctc agg atg ctc ctt tgt gac atc aaa ccc car ata aag acc agt gat
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Leu Arg Met Leu Leu Cys Asp Ile Lys Pro Gln Ile Lys Thr Ser Asp
cet tee act etg caa gte kar atk ttt tgt caa egt gaa gea gaa egg
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Pro Ser Thr Leu Gln Val Xaa Xaa Phe Cys Gln Arg Glu Ala Glu Arg
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                                                                      487
Cys Thr Gly Ala Ser Trp Gln Phe Ala Thr Asn Gly Glu Lys Ser Leu
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ctc ttt gac gca atg aac atg acc tgg aca gta att aat cat gaa gcc
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Leu Phe Asp Ala Met Asn Met Thr Trp Thr Val Ile Asn His Glu Ala
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                                    135
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Ser Xaa Ile Lys Glu Thr Trp Lys Lys Asp Arg Xaa Leu Glu Xaa Tyr
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Phe Arg Lys Leu Ser Lys Gly Asp Cys Asp His Trp Leu Arg Glu Phe
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190					195					200				-	205	
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Беп	261	Arg	-35	GIU	Cys	val	птэ	-30	ASP	Gry	Arg	vaı	-25	1111	Deu	
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Leu	Pne	45	Pne	Vai	Met	Asp	50	пув	vaı	AIA	Ald	55	ьeu	тър	FIIC	
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ccc c	tg cac	ttt	tct	gat	cta	att	tct	gtt	tta	tac	ctt	ata	ccc	aaa	210
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296

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Pro Leu Ser Pro Tyr Pro Lys Pro Gln Leu Gly Thr His Ala Gly Gln	
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Glu Ser Gly Xaa Val Tyr Asp Cys Val Lys Leu Thr Phe Ser Pro Ser	
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Thr Leu Leu Val Asn Ile Thr Asp Gln Val Tyr Glu Tyr Lys Tyr Lys	
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Phe Asn Asn Ser Leu Pro Asn Lys Asp Xaa Xaa Asn Asp Ile Met Leu	
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aca atc gca aaa tyc rrg gcs tva gag ggc ctc cga gac ccc tat ggc Thr Ile Ala Lys Xaa Xaa Ala Xaa Glu Gly Leu Arg Asp Pro Tyr Gly -80 -75 -70	160
cgc ctc tgt ggt agc gag cac ccc cga aga cca cct gag cgg ccc gag Arg Leu Cys Gly Ser Glu His Pro Arg Arg Pro Pro Glu Arg Pro Glu -65 -60 -55	208
gaa gac ccg agc act cca gag gag gcc tct acc acc cct gaa gaa gcc Glu Asp Pro Ser Thr Pro Glu Glu Ala Ser Thr Thr Pro Glu Glu Ala	256
-50 -45 -40 tog age act gec caa gea caa aag eet tea gtg eee egg age aat ttt	304
Ser Ser Thr Ala Gln Ala Gln Lys Pro Ser Val Pro Arg Ser Asn Phe -35 -20 -20	
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Gln Gly Thr Lys Lys Ser Leu Leu Met Ser Ile Leu Ala Leu Ile Phe -15 -10 -5	
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aag aar atc gtc aca gaa ran ttt gtg cgc aga ggg tac ctg att tat	496
Lys Lys Ile Val Thr Glu Xaa Phe Val Arg Arg Gly Tyr Leu Ile Tyr 30 40 45	
ara ccg gtg ccc cgt abc agt ccg gtg gag tat gas ttc ttc tgg ggg Xaa Pro Val Pro Arg Xaa Ser Pro Val Glu Tyr Xaa Phe Phe Trp Gly 50 55 60	544

ccc cga gca cac gtg gaa tcg agc ara ctg aaa stc wtg cat ttt gtg Pro Arg Ala His Val Glu Ser Ser Xaa Leu Lys Xaa Xaa His Phe Val 65 70 75	592
gca agg gtt cgt aac cga tgc tct aaa gac tgg cct tgt aat tat gac Ala Arg Val Arg Asn Arg Cys Ser Lys Asp Trp Pro Cys Asn Tyr Asp 80 85 90	640
tgg gat tcg gac gat gat gca gag gtt gag gct atc ctc aat tca ggt Trp Asp Ser Asp Asp Asp Ala Glu Val Glu Ala Ile Leu Asn Ser Gly 95 100	688
gct arg ggt tat tcc gcc cct taagtaratc tgaggcagac ccttgggggt Ala Xaa Gly Tyr Ser Ala Pro 110 115	739
gtaaaagaga gtcacaggta ccccaaggag tagatgccag ggtcctaagt tgaaaatgmt gtcgattggg ggcgggggac actgtatttg atatttgtga tcagtgatca ttgttcaact gcgaaataga gtgtttgctt ttgataatgg aaaattgtat tcgttttaaa attccgtttg ttgagaataa caatatgttt aaaaatataa ttgaacaaat tttaaaaaaa aaaamcccy	799 859 919 978
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gtk atg aac agc cgt ggc atc tgg ctc tcc tac gtg ctg gcc atc ggt Val Met Asn Ser Arg Gly Ile Trp Leu Ser Tyr Val Leu Ala Ile Gly -20 -15 -10	155
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530 590

650

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710
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atg aga act tta ttt ggt gca gtc agg gct cca ttt agt tcc ctc act
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Met Arg Thr Leu Phe Gly Ala Val Arg Ala Pro Phe Ser Ser Leu Thr
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                             -20
ctg ctt cta atc acc cct tct ccc agc cct ctt cta ttt gat aga ggt
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Leu Leu Leu Ile Thr Pro Ser Pro Ser Pro Leu Leu Phe Asp Arg Gly
ctg tcc ctc aga tca gca atg tct tagcccctct cctctctcc attccttcct
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Leu Ser Leu Arg Ser Ala Met Ser
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gttggtactc atttcttcta acttttaata aacatttagg tataatacat tacagtaagt
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rrrqqcacat gactqaaqta cctcaqctqc gcaqcctgta accagttttt ttaatgtaaa
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                                                                      120
atttgtagag aatcattttg gtgctcaagt ctcttagcag tgccttattg cctcatagca
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agaag atg ctg ggg ttt ttt ttg ttt ttg tcc ttt gta tta atg tat gat
      Met Leu Gly Phe Phe Leu Phe Leu Ser Phe Val Leu Met Tyr Asp
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                              -10
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Gly Leu Arg Leu Phe Gly Ile Leu Ser Thr Cys Arg Val His His Thr
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atg aat cag ttc cta att gat ata tct agc ttt acc tcc cga gtt aaa
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Met Asn Gln Phe Leu Ile Asp Ile Ser Ser Phe Thr Ser Arg Val Lys
                20
                                    25
aaa aaa atc ttt tta ttt tat gcc ttc awa ggt tgc ycg ttt car agt
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Lys Lys Ile Phe Leu Phe Tyr Ala Phe Xaa Gly Cys Xaa Phe Gln Ser
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Ala Thr
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        Met Ala Met Trp Asn Arg Pro Xaa Xaa Leu Pro Gln Gln
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Pro Leu Xaa Ala Glu Pro Thr Ala Glu Gly Glu Pro His Leu Pro Thr
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Gly Ile Ser Leu Ser Gln Leu Phe Pro Glu Pro Glu His Ser Ser Phe	•
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tgc aca gag ttc atg gca ggc ctg gtg ckm tgg ctg gag ttg tct gaa	302
Cys Thr Glu Phe Met Ala Gly Leu Val Xaa Trp Leu Glu Leu Ser Glu	
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Ala Val Leu Pro Thr Met Thr Ala Phe Ala Ser Gly Leu Gly Gly Glu	
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Gly Arg Pro Asp Gly Asp His Ser Gly Pro Ser Glu Leu Leu Thr Gln	
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Gly Trp Ala Leu	
75	
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Gly Pro Leu Met Leu Val Phe Thr Leu Val Ala Ile Leu Leu His Gly	
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	146
Met Lys Thr Ser Asp Thr Ile Ile Ara Glu Gly Thr Leu Met Gly Thr	146
Met Lys Thr Ser Asp Thr Ile Ile Arg Glu Gly Thr Leu Met Gly Thr -55 -45 -40	146
-55 -50 -45 -40	146 194
-55 -50 -45 -40 gcc att ggc acc tgc ttc ggc tac tgg ctg gga gtc tca tcc ttc att	
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	cta Leu		Met													482
	gta Val 75															530
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Ser Xaa			Gly					Leu					Thr		
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Asp Asn	GIY	125	Asp	GIY	Deu	116	130	PIO	naa	Буб	Add	135	1111	PIO	
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Arg Ile		_			_		_	_	_	_			_		133
· 9 11C	p	, 41	10		••••9	201		15			0	9	20		`,
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ctg agg Leu Arg	Leu					Ser	Asn	Ala	Tyr	Ser					
Leu Arg	Leu 40	Leu	Gly	Ser	Leu	Ser 45			_		50	Arg	His	Tyr	297
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110

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Gly Pro Phe Cys Ala Ser Phe Pro Ser Gly Xaa Leu Ser Pro Pro Gly 25 30 35	
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Asn		Glu	Thr	Glu	Ala		Glu	Leu	Leu	Lys		Arg	Arg	Arg	Arg	
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Trp Arg Thr Ile Ser Met Gly Pro Cys Ala Arg Gly Ser Pro Met Asn
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Lys Ala Asn Xaa Ala Ala Ser Xaa Gln 60 65	
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tgaatgaaaa taaagctttg acttcaaaaa aagccagaat tgatccata atg gaa gaa	238
Met Glu Glu	
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ata agt tot coa ott gta gaa ttt gta aaa gtt ttg tgo acc aac cag	286
Ile Ser Ser Pro Leu Val Glu Phe Val Lys Val Leu Cys Thr Asn Gln	
-20 -15 -10	
gtt ctc att act gcc agg gct gtg cct aca aaa aag gca tct gtg cga	334
Val Leu Ile Thr Ala Arg Ala Val Pro Thr Lys Lys Ala Ser Val Arg	
-5 1 5	
tgt gtg gaa aaa agg ttt tgg ata cca aaa act aca agc aaa cat ctg	382
Cys Val Glu Lys Arg Phe Trp Ile Pro Lys Thr Thr Ser Lys His Leu	
10 15 20 25	420
tot aga tgt att gat gga att tot ggo ttt ota aat gat ttt act tto	430
Ser Arg Cys Ile Asp Gly Ile Ser Gly Phe Leu Asn Asp Phe Thr Phe	
	470
tgc ctt gaa ttt tca agg cat aga tgt caa ctt aca gaa taacatgtkt	479
Cys Leu Glu Phe Ser Arg His Arg Cys Gln Leu Thr Glu 45 50	
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aaacagcaac agtgtaacta gtcttttgtt gtaaatggtt attttcctta taaaaatttt	599
aaaaactaag tggcaaattc catgaaaata tttctcagtt ctgtatgcac ttttatttaa	659
cattattcat ataattctcc ccccaccact ttatttat	719
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tatataaatg tttcaagcca ttattgctga atggttcttt agttattaac ctagacccaa	899
atcaaagacc agttggattt atgatatttt ttatttgttc ttgcagccaa agtgccagtt	959
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Glu Cys Ile Asp Trp Ser Glu Arg Arg Asn Ala Val Ala Ser Val Val

110

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	a ttg ttt t					
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	yr Pro Lys P					
102 102 -	5		10		15	-7-
	tt tcc aca t					
_	ne Ser Thr L		Phe Met			Asn
20		25	~~~ ~~~ .	30		aca 350
-	tg aga ggt g al Arg Gly A					
35	i mig oi,	40	014 001	45	-u v=,j	
	ga gtt tgg c					
_	rg Val Trp L				et Phe Gly	
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	ct tcc atg t la Ser Met T					
neu lie Al	70	ip ile beu	75	Ala iyi vo	80	ASII
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Thr Asp Va	al Tyr Pro G	ly Leu Ala		Phe Gln As		Ile
	85		90		95	5.10
	gc act ctg a er Thr Leu I					
10		105	rne dry A	Arg ini di 11		IIP
	cact tottaa		tcctt ttg	ttatatt ct	gtttgtag	595
Thr			_			
	tatctctcag	_			•	_
-	a catttttatg a gactgttaat		-			
_	atteetgaga	_	_	_		- 3 - 3
	tagaagtaac					
	c actttgggag	_				
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	ctgtaatccc					
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ctg cgc ttc ctg agg gct gac ggc gac ctg acg cta cta tgg gcc gag Leu Arg Phe Leu Arg Ala Asp Gly Asp Leu Thr Leu Leu Trp Ala Glu -5 1 5 10	149
tgg cag gga cga cgc cca gaa tgg gag ctg act gat atg gtg gtg tgg Trp Gln Gly Arg Arg Pro Glu Trp Glu Leu Thr Asp Met Val Val Trp 15 20 25	197
gtg act gga gcc tcg agt gga att ggt gag gag ctg gct tac cag ttg Val Thr Gly Ala Ser Ser Gly Ile Gly Glu Glu Leu Ala Tyr Gln Leu 30 35 40	245
tct aaa cta gga gtt tct ctt gtg ctg tca gcc aga aga gtg cat gag Ser Lys Leu Gly Val Ser Leu Val Leu Ser Ala Arg Arg Val His Glu 45 50 55	293
ctg gaa agg gtg aaa aga aga tgc cta gag aat ggc aat tta aaa gaa Leu Glu Arg Val Lys Arg Arg Cys Leu Glu Asn Gly Asn Leu Lys Glu 60 65 70	341
aaa gat ata ctt gtt ttg ccc ctt gac ctg acc gac act ggt tcc cat Lys Asp Ile Leu Val Leu Pro Leu Asp Leu Thr Asp Thr Gly Ser His 75 80 85 90	389
gaa agc ggc tac caa agc tgt tct cca gga att tgg tagaatcgac Glu Ser Gly Tyr Gln Ser Cys Ser Pro Gly Ile Trp 95	435
attotggtca acaatgtgga aatgtcccag cgttctctgt gcatggatac caacttggat	495
gtctacagaa agctaatgag agcttaacta cttagggacg gtgtccttga caaaatgtgk	5 5 5
kctgcctcac atgatcgaga ngaarcaagg aaagattgtt actgtgaata gcatcctggg	615
tatcatatct gtacctcttt ccattggata ctgtgctagc aagcatgctc tccggggktk	675
ktttaatggc cttcraacag aacttgccac atacccargt ataatagttt ctaacatttg	735
cccaggacct gtgcaatcaa atattgtgga aaattcccta gctggagaag tcacaaagac	795 855
tataggcaat aatggagacc agtcccacaa gatgacaacc agtcgttgtg tgcggctgat	915
gttaatcage atggecaatg atttgaaaga agtttggate teagaacaae etttettgtt agtaacatat ttgtggeaat acatgecaae etgggeetgg tggataacea acaagatggg	975
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Pro Cys Leu Asp
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Arg Lys Ser Cys His Asp Trp Ile Gly Pro Pro Asp Lys Tyr Ser Asn
           30 35 40
Leu Arg Pro Val His Phe Tyr Ile Pro Glu Asn Glu Ser Pro Leu Glu
      45 50
Gln Lys Leu Arg Lys Leu Arg Gln Glu Thr Gln Glu Trp Asn Gln Gln
                   65
                           70
Phe Trp Ala Asn Gln Asn Leu Thr Phe Ser Lys Glu Lys Glu Glu Phe
  75 80
                      85
Ile His Ser Arg Leu Lys Thr Lys Gly Leu Gly Leu Arg Thr Glu Ser
90 95 100 105
Gly Gln Lys Ala Thr Leu Asn Ala Glu Glu Met Ala Asp Phe Tyr Lys
           110 115 120
Glu Phe Leu Ser Lys Asn Phe Gln Lys His Met Tyr Tyr Asn Arg Asp
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Asn 170

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Asn Ala Ile Ala Val Leu His Glu Glu Arg Phe Leu Lys Asn Ile Gly 5 10 10 15 15 17  

Trp Gly Thr Asp Gln Gly Ile Gly Gly Phe Gly Glu Glu Pro Gly Ile 20 25 30  

Lys Ser Xaa Xaa Met Xaa Leu Ile Arg Ser Val Arg Thr Val Met Arg 35 40 45 50  

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Phe Gly
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Arg Pro Ala Ser Ala Ala Pro Met Gly Gly Pro Glu Leu Ala Gln His
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Glu Glu Leu Thr Leu Leu Phe His Gly Thr Leu Gln Leu Gly Gln Ala
           15
                                20
Leu Asn Gly Val Tyr Arg Thr Thr Glu Gly Arg Leu Thr Lys Ala Arg
                            35
Asn Ser Leu Gly Leu Tyr Gly Arg Thr Ile Glu Leu Leu Gly Gln Glu
                       50
Val Ser Arg Gly Arg Asp Ala Ala Gln Glu Leu Arg Ala Ser Leu Leu
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Glu Thr Gln Met Glu Glu Asp Ile Leu Xaa Leu Gln Ala Xaa Ala Thr
                                   85
Ala Glu Val Leu Gly Glu Val Ala Gln Ala Gln Lys Val Leu Arg Asp
                                100
Ser Val Gln Arg Leu Xaa Xaa Gln Leu Xaa Xaa Ala Trp Leu Gly Pro
                            115
                                               120
Ala Tyr Arg Lys Phe Glu Val Leu Lys Ala Pro Pro Xaa Lys Gln Asn
                        130
                                           135
His Ile Leu Trp Ala Leu Thr Gly His Val Xaa Arg Gln Xaa Arg Glu
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Met Val Ala Gln Gln Xaa Xaa Leu Xaa Gln Ile Gln Glu Lys Leu His
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       -35 -30 -25·
Arg Ile Lys Gly Phe Ile Ala Cys Phe Ala Ile Gly Ile Leu Cys Ser
       -20 -15
Leu Leu Gly Thr Val Leu Leu Trp Val Pro Arg Lys Gly Leu His Leu
   -5 1
Phe Ala Val Phe Tyr Thr Phe Gly Asn Ile Ala Ser Ile Gly Ser Thr
                       20
    15
Ile Phe Leu Met Gly Pro Val Lys Gln Leu Lys Arg Met Phe Glu Pro
          30
                       35
Thr Arg Leu Ile Ala Thr Ile Met Val Leu Leu Cys Phe Ala Leu Thr
                       50
Leu Cys Ser Ala Phe Trp Trp His Asn Lys Gly Leu Ala Leu Ile Phe
                   65
Cys Ile Leu Gln Ser Leu Ala Leu Thr Trp Tyr Ser Leu Ser Phe Ile
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Pro Phe Ala Arg Asp Ala Val Lys Xaa Cys Phe Ala Val Cys Leu Ala
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Phe Pro Gly Thr Ser Ser Phe Ile Val Ala Leu Ser Ser Pro Ala Asp

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Ala Asp Ser Thr Ile Met Asp Ile Gln Val Pro Thr Arg Ala Pro Asp
 15 20
Ala Val Tyr Thr Glu Leu Gln Pro Thr Ser Pro Thr Pro Thr Trp Pro
 30 35
Ala Asp Glu Thr Pro Gln Pro Gln Thr Gln Thr Gln Gln Leu Glu Gly
 45 50
                                    55
Thr Asp Gly Pro Leu Val Thr Asp Pro Glu Thr His Xaa Ser Xaa Lys
                                 70
60 65
Ala Ala His Pro Thr Asp Asp Thr Thr Thr Leu Ser Glu Arg Pro Ser
          80
                             85
Pro Ser Thr Xaa Val His Xaa Arg Pro Xaa Xaa Pro Ser Xaa His Leu
    95 100
Val Phe Met Arg Met Thr Pro Ser Ser Met Met Asn Thr Pro Ser Gly
                       115
Asn Xaa Gly Cys Trp Ser Gln Leu Cys Cys Ser Ser Gln Ala Ser Ser
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                 130
Ser Ser Pro Val Ala Ser Ala Gly Ser Cys Pro Gly Tyr Ala Gly Ile
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Ile Ala Gly Glu Ser Ile Arg Asn Arg Ser
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                  -5
Leu Leu Gln Ser Pro Gly Leu Thr Trp Ser Leu Glu Val Pro Thr Gly
     10
                           15
Arg Glu Gly Lys Glu Gly Gly Asp Arg Gly Pro Gly Leu Xaa Gly Ala
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Thr Pro Ala Arg Ser Pro Gln Gly Lys Glu Met Gly Arg Gln Arg Thr
                     45
                                         50
Arg Lys Val Lys Gly Pro Ala Trp Xaa His Thr Ala Asn Gln Glu Leu
                   60
                                     65
Asn Arg Met Arg Ser Leu Ser Ser Gly Ser Val Pro Val Gly His Leu
                                  80
               75
Glu Gly Gly Thr Val Lys Leu Gln Lys Asp Thr Gly Leu His Ser Cys
                              95
Xaa Asp Gly Met Ala Ser Leu Glu Gly Thr Pro Ala Ser Val Leu Ala
                         110
       105
Asp Ala Cys Pro Gly Phe His Asp Val Xaa Val Gln Xaa Ala Leu Phe
                     125
                                130
Gly Leu Ser Gly Xaa Xaa Leu Trp Leu Lys Thr His Phe Cys Leu Ser
                                      145
Ile Xaa Leu
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               - 35
Thr Val Ala Thr Ala Gly Val Val Thr Ser Val Ala Phe Met Leu Thr
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Leu Pro Ile Leu Val Cys Lys Val Gln Asp Ser Asn Arg Arg Lys Met
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Leu Pro Thr Gln Phe Leu Phe Leu Leu Gly Val Leu Gly Ile Phe Gly
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Leu Thr Phe Ala Phe Ile Ile Gly Leu Asp Gly Ser Thr Gly Pro Thr
                                  35
Arg Phe Phe Leu Phe Gly Ile Leu Phe Ser Ile Cys Phe Ser Cys Leu
                              50
Leu Ala His Ala Val Ser Leu Thr Lys Leu Val Arg Gly Arg Lys Ala
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Pro Phe Pro Val Gly Asp Ser Gly Ser Gly Arg Gly Leu Gln Pro Ser Pro Gly Cys Tyr Arg Tyr <210> 389 <211> 236 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -31..-1 <400> 389 Met Leu Ser Lys Gly Leu Lys Arg Lys Arg Glu Glu Glu Glu Lys -25 Glu Pro Leu Ala Val Asp Ser Trp Trp Leu Asp Pro Gly His Ala Ala -10 ~ 5 Val Ala Gln Ala Pro Pro Ala Val Ala Ser Ser Ser Leu Phe Asp Leu 10 Ser Val Leu Lys Leu His His Ser Leu Gln Xaa Ser Xaa Pro Asp Leu 25 Arg His Leu Val Leu Val Xaa Asn Thr Leu Arg Arg Ile Gln Ala Ser 45 40 Met Ala Pro Ala Ala Ala Leu Pro Pro Val Pro Thr Pro Pro Ala Ala 60 55 Pro Xaa Val Ala Asp Asn Leu Leu Ala Ser Ser Asp Ala Ala Leu Ser 75 Ala Ser Met Ala Xaa Leu Leu Glu Asp Leu Ser His Ile Glu Gly Leu 90 Ser Gln Ala Pro Gln Pro Leu Ala Asp Glu Gly Pro Pro Gly Arg Ser 105 Ile Gly Gly Xaa Pro Pro Xaa Leu Gly Ala Leu Asp Leu Leu Gly Pro 120 Ala Thr Gly Cys Leu Leu Asp Asn Gly Leu Glu Gly Leu Phe Glu Asp 140 135 Ile Asp Thr Ser Met Tyr Asp Asn Glu Leu Trp Ala Pro Ala Ser Glu 155 150 Gly Leu Lys Pro Gly Pro Glu Asp Gly Pro Gly Lys Glu Glu Ala Pro 175 170 Glu Leu Asp Glu Ala Glu Leu Asp Tyr Leu Met Asp Val Leu Val Gly 180 185 Thr Gln Ala Leu Glu Arg Pro Pro Gly Pro Gly Arg 200 <210> 390 <211> 149 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -100..-1 <400> 390

Met Glu Thr Leu Tyr Arg Val Pro Phe Leu Val Leu Glu Cys Pro Asn

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Leu Lys Leu Lys Lys Pro Pro Trp Leu His Met Pro Ser Ala Met Thr
            -80
                  -75
Val Tyr Ala Leu Val Val Val Ser Tyr Phe Leu Ile Thr Gly Gly Ile
                                          -55
         -65
              -60
Ile Tyr Asp Val Ile Val Glu Pro Pro Ser Val Gly Ser Met Thr Asp
      -50 -45
Glu His Gly His Gln Arg Pro Val Ala Phe Leu Ala Tyr Arg Val Asn
                   -30
                                    -25
Gly Gln Tyr Ile Met Glu Gly Leu Ala Ser Ser Phe Leu Phe Thr Met
                      -10
-20 -15
Gly Gly Leu Gly Phe Ile Ile Leu Asp Gly Ser Asn Ala Pro Asn Ile
                  5
       1
Pro Lys Leu Asn Arg Phe Leu Leu Phe Ile Gly Phe Val Cys Val
               20
Leu Xaa Ser Phe Xaa Xaa Ala Arg Val Phe Met Arg Met Lys Leu Pro
                  35
Gly Tyr Leu Met Gly
45
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<210> 391
<211> 69
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -49..-1
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<210> 392
<211> 241
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -30..-1
<400> 392
Met Gly Thr Ala Ser Arg Ser Asn Ile Ala Arg His Leu Gln Thr Asn
                          -20 -15
           -25
Leu Ile Leu Phe Cys Val Gly Ala Val Gly Ala Cys Thr Leu Ser Val
            -10
                                - 5
Thr Gln Pro Trp Tyr Leu Glu Val Asp Tyr Thr His Glu Ala Val Thr
                        10
Ile Lys Cys Thr Phe Ser Ala Thr Gly Cys Pro Ser Glu Gln Pro Thr
                     25
```

Cys Leu Trp Phe Arg Tyr Gly Ala His Gln Pro Glu Asn Leu Cys Leu 40 45 Asp Gly Cys Lys Ser Glu Ala Xaa Lys Phe Thr Val Arg Glu Ala Leu 55 60 Lys Glu Asn Gln Val Ser Leu Thr Val Asn Arg Val Thr Ser Asn Asp 75 Ser Ala Ile Tyr Ile Cys Gly Ile Ala Phe Pro Ser Val Pro Glu Ala 90 Arg Ala Lys Gln Thr Gly Gly Gly Thr Thr Leu Val Val Arg Glu Ile 105 Lys Leu Leu Ser Lys Glu Leu Arg Ser Phe Leu Thr Ala Leu Val Ser 115 120 125 Leu Leu Ser Val Tyr Val Thr Gly Val Cys Val Ala Phe Ile Leu Leu 135 140 145 Ser Lys Ser Lys Ser Asn Pro Leu Arg Asn Lys Glu Ile Lys Glu Asp 150 155 Ser Gln Lys Lys Ser Ala Arg Arg Ile Phe Gln Glu Ile Ala Gln 175 165 170 Glu Leu Tyr His Lys Arg His Val Glu Thr Asn Gln Gln Ser Glu Lys 185 190 Asp Asn Asn Thr Tyr Glu Asn Arg Arg Val Leu Ser Asn Tyr Glu Arg 195 200 205 Pro

<210> 393 <211> 47 <212> PRT <213> Homo sapiens

<221> SIGNAL <222> -30..-1

<400> 393

<210> 394 <211> 65 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -28..-1

Ser

<210> 395

<211> 73

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -24..-1

<400> 395

Met Thr Cys Trp Met Leu Pro Pro Ile Ser Phe Leu Ser Tyr Leu Pro -20 -15

Leu Trp Leu Gly Pro Ile Trp Pro Cys Ser Gly Ser Thr Leu Gly Lys

Pro Asp Pro Gly Val Trp Pro Ser Leu Phe Arg Pro Trp Asp Ala Ala 15

Ser Pro Gly Asn Tyr Ala Leu Ser Arg Gly Xaa Asn Xaa Tyr Xaa Xaa 30 35

Trp Gly Gln Gly Thr His Ser Ser Leu

45

<210> 396

<211> 60

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -18..-1

<400> 396

Met Pro Cys Pro Thr Trp Thr Cys Leu Lys Ser Phe Pro Ser Pro Thr -10 -15

Ser Ser His Ala Ser Ser Leu His Leu Pro Pro Ser Cys Thr Arg Leu 10

Thr Leu Thr Gln Thr Leu Arg Thr Gly Met His Leu Ser Arg Ala Leu 20 25 30

Gln Gly Thr Leu Thr Arg Leu Gln Ser Thr Pro Ala

<210> 397

<211> 192

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -93..-1

<400> 397

Met Ala Glu Leu Gly Leu Asn Glu His His Gln Asn Glu Val Ile Asn -85

Tyr Met Arg Phe Ala Arg Ser Lys Arg Gly Leu Arg Leu Lys Thr Val

-70 -65 -75 Asp Ser Cys Phe Gln Asp Leu Lys Glu Ser Arg Leu Val Glu Asp Thr -60 ~55 -50 Phe Thr Ile Asp Glu Val Ser Glu Val Leu Asn Gly Leu Gln Ala Val -40 - 35 Val His Ser Glu Val Glu Ser Glu Leu Ile Asn Thr Ala Tyr Thr Asn -25 -20 -15 Val Leu Leu Arg Gln Leu Phe Ala Gln Ala Glu Lys Trp Tyr Leu -10 -5 1 Lys Leu Gln Thr Asp Ile Ser Glu Leu Glu Asn Arg Glu Leu Leu Glu 10 15 Gln Xaa Ala Glu Phe Glu Lys Ala Xaa Ile Thr Ser Ser Asn Lys Lys 25 30 Pro Ile Leu Xaa Val Thr Xaa Pro Lys Leu Ala Pro Leu Asn Glu Gly 45 40 Gly Thr Ala Lys Leu Leu Asn Lys Val Ile Cys Ile Ile Leu Arg Asn **、5**5 Gly Lys Ser Leu Ile Leu Ser Cys His Cys Leu Gly Trp Arg Asn Lys 70 75 Ser Gly Arg Phe Val Ser Gly Pro Leu Arg Ile Ile Ser Pro Leu Gln 90

<210> 398

<211> 149

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -72..-1

<400> 398

Met Asn Leu Phe Ile Met Tyr Met Ala Gly Asn Thr Ile Ser Ile Phe
-70 -65 -60

Pro Thr Met Met Val Cys Met Met Ala Trp Arg Pro Ile Gln Ala Leu
-55 -50 -45

Met Ala Ile Ser Ala Thr Phe Lys Met Leu Glu Ser Ser Ser Gln Lys
-40 -35 -30 -25

Phe Leu Gln Gly Leu Val Tyr Leu Ile Gly Asn Leu Met Gly Leu Ala -20 -15 -10

Leu Ala Val Tyr Lys Cys Gln Ser Met Gly Leu Leu Pro Thr His Ala
-5 1 5

Ser Asp Trp Leu Ala Phe Ile Glu Pro Pro Glu Arg Met Glu Ser Val 10 15 20

Val Glu Asp Cys Phe Cys Glu His Glu Lys Ala Ala Pro Gly Pro Tyr 30 35 40

Val Phe Gly Ser Tyr Leu His Pro Ser Leu Ser Pro Val Ala Pro Gln
45 50 55

His Thr Leu Lys Leu Ile Thr Tyr Val Lys Lys Asn Gln Lys Thr Leu 60 65 70

Phe Ser Met Val Gly

75

<210> 399

<211> 73

<212> PRT

<213> Homo sapiens

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<220>
<221> SIGNAL
<222> -20..-1
<400> 399
Met Thr Pro Leu Leu Thr Leu Ile Leu Val Val Leu Met Gly Leu Pro
   -15 -10 -5
Leu Ala Gln Ala Leu Asp Cys His Val Cys Ala Tyr Asn Gly Asp Asn
Cys Phe Asn Pro Met Arg Cys Pro Ala Met Val Ala Tyr Cys Met Thr
   15
                       20
                                         25
Thr Arg Thr Tyr Tyr Thr Pro Thr Arg Met Lys Val Ser Lys Ser Cys
                     35
Val Pro Arg Cys Phe Glu Xaa Cys Val
45 50
<210> 400
<211> 86
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -20..-1
<400> 400
Met Asn Leu His Phe Pro Gln Trp Phe Val His Ser Ser Ala Leu Gly
-20 . -15
                                 -10
Leu Val Leu Ala Pro Pro Phe Ser Ser Pro Gly Thr Asp Pro Thr Phe
            1
Pro Cys Ile Tyr Cys Arg Leu Leu Asn Met Ile Met Thr Arg Leu Ala
                        20
Phe Ser Phe Ile Thr Cys Leu Cys Pro Asn Leu Lys Glu Val Cys Leu
                   35
                               40
Ile Leu Pro Glu Lys Asn Cys Asn Ser Arg His Ala Gly Phe Val Gly
                               5.5
Pro Xaa Lys Leu Arg Gln
<210> 401
<211> 78
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 401
Met Cys Pro Val Phe Ser Lys Gln Leu Leu Ala Cys Gly Ser Leu Leu
  -20 -15 -10
Pro Gly Leu Trp Gln His Leu Thr Ala Asn His Trp Pro Pro Phe Ser
Xaa Phe Leu Cys Thr Val Cys Ser Gly Ser Ser Glu Gln Ile Ser Glu
```

Tyr Thr Ala Ser Ala Thr Pro Pro Leu Cys Arg Ser Leu Asn Gln Glu 30 35 40

Pro Phe Val Ser Arg Ala Ile Arg Pro Lys Tyr Ser Ile Thr

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45 50 55

<210> 402 <211> 65

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -28..-1

<400> 402

Met Gly Lys Gly His Gln Arg Pro Trp Lys Val Leu Pro Leu Ser
-25 -20 -15

Cys Phe Leu Val Ala Leu Ile Ile Trp Cys Tyr Leu Arg Glu Glu Ser
-10 -5 1

Glu Ala Asp Gln Trp Leu Arg Gln Val Trp Gly Glu Val Pro Glu Pro 5 10 15 20 Ser Asp Arg Ser Glu Glu Pro Glu Thr Pro Ala Ala Tyr Arg Ala Arg

30

Thr

<210> 403

<211> 211

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -27..-1

<400> 403

Met Leu Leu Ser Ile Thr Thr Ala Tyr Thr Gly Leu Glu Leu Thr
-25 -20 -15

Phe Phe Ser Gly Val Tyr Gly Thr Cys Ile Gly Ala Thr Asn Lys Phe
-10 -5 1 5

Gly Ala Glu Glu Xaa Ser Leu Ile Gly Leu Ser Gly Ile Phe Ile Gly
10 15 20

Ile Gly Glu Ile Leu Gly Gly Ser Leu Phe Gly Leu Leu Ser Lys Asn 25 30 35

Asn Arg Phe Gly Arg Asn Pro Val Val Leu Leu Gly Ile Leu Val His
40 45 50

Phe Ile Ala Phe Tyr Leu Ile Phe Leu Asn Met Pro Gly Asp Ala Pro 55 60 65

Ile Ala Pro Val Lys Gly Thr Asp Ser Ser Ala Tyr Ile Lys Ser Ser 70 80 85

Lys Xaa Phe Ala Ile Leu Cys Xaa Phe Leu Xaa Gly Leu Gly Asn Ser 90 95 100

Cys Phe Asn Thr Xaa Leu Leu Xaa Ile Xaa Gly Phe Leu Tyr Ser Glu

Xaa Ser Ala Pro Xaa Phe Ala Ile Phe Asn Phe Val Gln Ser Ile Cys
120 125 130

Ala Ala Val Ala Phe Phe Tyr Ser Asn Tyr Leu Leu Leu His Trp Gln
135 140 145

Leu Leu Val Met Val Ile Phe Gly Phe Xaa Gly Thr Ile Ser Phe Phe 150 165 160

Thr Val Glu Trp Glu Xaa Ala Ala Phe Val Xaa Arg Gly Ser Asp Tyr 170 175 180 Arg Ser Ile

<210> 404 <211> 123 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -80..-1 <400> 404 Met Ser Thr Trp Tyr Leu Ala Leu Asn Lys Ser Tyr Lys Asn Lys Asp ~80 -75 -70 Ser Val Arg Ile Tyr Leu Ser Leu Cys Thr Val Ser Ile Lys Phe Thr -60 -55 -50 Tyr Phe His Asp Ile Gln Thr Asn Cys Leu Thr Thr Trp Lys His Ser -45 -40 -35 Arg Cys Arg Phe Tyr Trp Ala Phe Gly Gly Ser Ile Leu Gln His Ser -20 -30 -25 Val Asp Pro Leu Val Leu Phe Leu Ser Leu Ala Leu Leu Val Thr Pro -15 -10 -5 Thr Ser Thr Pro Ser Ala Lys Ile Gln Ser Leu Gln Ile Asp Leu Pro 1 5 10 Gly Gly Trp Arg Leu Ala Thr Asp Arg Ile Phe Thr Leu Ser Pro Val 20 25 Pro Met Asp Xaa Pro Leu Ile Leu His Gln Leu 35 40

<210> 405 <211> 86 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -26..-1

<400> 405
Met Glu Lys Ser Trp Met Leu Trp Asn Phe Val Glu Arg Trp Leu Ile

<210> 406 <211> 162 <212> PRT <213> Homo sapiens

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<220>
<221> SIGNAL
<222> -31..-1
<400> 406
Met Ala Ala Ala Trp Pro Ser Gly Pro Xaa Ala Pro Glu Ala Val Thr
                            -20
                 -25
Ala Arg Leu Val Gly Val Leu Trp Phe Val Ser Val Thr Thr Gly Pro
                           ~5
                -10
Trp Gly Ala Val Ala Thr Ser Ala Gly Gly Glu Glu Ser Leu Lys Cys
                        10
   5
Glu Asp Leu Lys Val Gly Gln Tyr Ile Cys Lys Asp Pro Lys Ile Asn
                                  30
                     25
Asp Ala Thr Gln Glu Pro Val Asn Cys Thr Asn Tyr Thr Ala His Val
                               45
                 40
Ser Cys Phe Pro Ala Pro Asn Ile Thr Cys Lys Asp Ser Ser Gly Asn
                                60
             55
Glu Thr His Phe Thr Gly Asn Glu Val Gly Phe Phe Lys Pro Ile Ser
                               75
            70
Cys Arg Asn Val Asn Gly Tyr Ser Tyr Asn Glu Gln Ser His Val Ser
                    90
         85
Phe Ser Trp Met Val Gly Ser Arg Ser Ile Leu Pro Trp Ile Pro Cys
                    105
                                110
    100
Phe Gly Phe Val Lys Xaa Xaa His Cys Arg Val Xaa Trp Asn Trp Glu
  115
                    120
Pro Asn
130
<210> 407
<211> 98
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 407
Met Ala Ser Leu Leu Cys Cys Gly Pro Lys Leu Ala Ala Cys Gly Ile
-35
          -30
                               -25
Val Leu Ser Ala Trp Gly Val Ile Met Leu Ile Met Leu Gly Ile Phe
                    -15
                                      -10
Phe Asn Val His Ser Ala Val Leu Ile Glu Asp Val Pro Phe Thr Glu
                1
                               5
Lys Asp Phe Glu Asn Gly Pro Gln Asn Ile Tyr Asn Leu Tyr Xaa Gln
                                    25
       15
                            20
Xaa Ser Tyr Asn Cys Phe Ile Ala Ala Gly Leu Tyr Leu Leu Leu Gly
                        35
                                   . 40
Gly Phe Ser Phe Cys Gln Xaa Arg Leu Asn Lys Arg Lys Glu Tyr Met
                 50
                                     55
Val Arg
60
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<210> 408 <211> 70 <212> PRT

<213> Homo sapiens

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<220>
<221> SIGNAL
<222> -15..-1
<400> 408
Met Arg Phe Leu Pro Cys Cys Leu Leu Trp Ser Val Phe Asn Pro Glu
                -10
                                 -5
Ser Leu Asn Cys His Tyr Phe Xaa Xaa Glu Xaa Cys Ile Phe Xaa Ser
                                        15
                        10
Leu Gln Tyr Tyr Glu Ile Ser Leu Gln Glu Lys Leu Leu Gly Phe Leu
 20
                 25
                                   30
Trp Leu Cys Phe Leu Ser Tyr Phe Phe Arg Ala Val Tyr Phe Leu Ile
 35 40
Asp Phe Ser Ser Phe Thr
<210> 409
<211> 60
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -45..-1
<400> 409
Met His Ser Leu Phe Ile Ala Ser Leu Lys Val Leu Phe Tyr Tyr Ser
-45 -40 -35 -30
Phe Ser Phe Arg Phe Asn Trp Phe Asp Cys Leu Leu His Asn Leu Gly
           -25
                           -20
Glu Asn Phe Leu Ser Leu Leu Ser Lys Ser Cys Ser Ala Asp Pro Ser
                 -5
Gly Ser Thr Phe Met Arg Asp Ile Glu Thr Asn Lys
                   10
<210> 410
<211> 39
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -22..-1
<400> 410
Met Pro Glu Ala Val Glu Gln Ser Ala His Leu Phe Val Thr Trp Ser
     -20 <del>-</del>15
                            -10
Ser Gln Arg Ala Leu Ser His Pro Ala Pro Phe Leu Thr Xaa Xaa Lys
                       5 . 10
          1
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<210> 411 <211> 51 <212> PRT

Asn Pro Phe Leu Trp Lys Leu 15

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<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 411
Met Ala Phe Gln Ser Leu Leu Glu Met Lys Phe Phe Leu Cys Ala Ala
   -20
               -15
                              -10
Phe Pro Leu Gly Ala Gly Val Lys Met Phe His Tyr Leu Gly Pro Gly
                   1
                             5
Lys Pro Leu Xaa Gln Ala Ser Pro Ser Pro His Pro His Arg Xaa Arg
                      20
10
              15
Ile Trp Pro
<210> 412
<211> 95
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -48..-1
<400> 412
Met Ala Ser Ser His Trp Asn Glu Thr Thr Thr Ser Val Tyr Gln Tyr
   ~45 ~40 -35
Leu Gly Phe Gln Val Gln Lys Ile Tyr Pro Phe His Asp Asn Trp Asn
-30 -25 -20
Thr Ala Cys Phe Val Ile Leu Leu Leu Phe Ile Phe Thr Val Val Ser
 -15 -10 -5
Leu Val Val Leu Ala Phe Leu Tyr Glu Val Leu Xaa Xaa Cys Cys
                 10
1 5
Val Lys Asn Lys Thr Val Lys Asp Leu Lys Ser Glu Pro Asn Pro Leu
    20
                      25
Xaa Xaa Met Met Asp Asn Ile Arg Lys Arg Glu Thr Glu Val Val
                     40
<210> 413
<211> 60
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -32..-1
<400> 413
Met Asp Glu Tyr Ser Trp Trp Cys His Val Leu Glu Val Val Lys Gly
 -30
                     -25
                                      -20
Gln Met Phe Thr Phe Ile Asn Ile Thr Leu Trp Leu Gly Ser Leu Cys
 -15 -10 -5
Gln Arg Phe Phe Tyr Ala Ser Gly Thr Tyr Phe Leu Ile Tyr Ile Ser
                10
1 5
Thr Val Thr Pro Ser Trp Arg Leu Cys Leu Val Ser
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<210> 414
<211> 170
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -79..-1
<400> 414
Met Glu Asp Pro Asn Pro Glu Glu Asn Met Lys Gln Gln Asp Ser Pro
           -75
                                  -70
Lys Glu Arg Ser Pro Gln Ser Pro Gly Gly Asn Ile Cys His Leu Gly
                               -55
Ala Pro Lys Cys Thr Arg Cys Leu Ile Thr Phe Ala Asp Ser Lys Phe
                           -40
Gln Glu Arg His Met Lys Arg Glu His Pro Ala Asp Phe Val Ala Gln
                       -25
                                          -20
Lys Leu Gln Gly Val Leu Phe Ile Cys Phe Thr Cys Ala Arg Ser Phe
-15
                   ~10
Pro Ser Ser Lys Ala Xaa Xaa Thr His Gln Arg Ser His Gly Pro Xaa
                               10
Ala Lys Pro Thr Leu Pro Val Ala Thr Thr Ala Gln Pro Thr Phe
                           25
Pro Cys Pro Asp Cys Gly Lys Thr Phe Gly Gln Ala Val Ser Leu Xaa
                       40
Arg His Xaa Gln Xaa His Glu Val Arg Ala Pro Pro Gly Thr Phe Ala
                   55
Cys Thr Xaa Cys Gly Gln Asp Phe Ala Gln Glu Xaa Gly Leu His Gln
              70
                                  75
His Tyr Ile Arg His Ala Arg Gly Gly Leu
          85
<210> 415
<211> 190
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -82..-1
Met Tyr Val Trp Pro Cys Ala Val Val Leu Ala Gln Tyr Leu Trp Phe
                           -75
     -80
His Arg Arg Ser Leu Pro Gly Lys Ala Ile Leu Glu Ile Gly Ala Gly
                       -60
                                          -55
Val Ser Leu Pro Gly Ile Leu Ala Ala Lys Cys Gly Ala Glu Val Ile
                   -45
                                      -40
Leu Ser Asp Ser Ser Glu Leu Pro His Cys Leu Glu Val Cys Arg Gln
               -30
                                   -25
Ser Cys Gln Met Asn Asn Leu Pro His Leu Gln Val Val Gly Leu Thr
           -15
                        -10
Trp Gly His Ile Ser Trp Asp Leu Leu Ala Leu Pro Pro Gln Asp Ile
Ile Leu Ala Ser Asp Val Phe Phe Glu Pro Glu Xaa Phe Glu Asp Ile
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25

40

Leu Ala Thr Ile Tyr Phe Leu Met His Lys Asn Pro Lys Val Gln Leu

<210> 416 <211> 114 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> ~60..-1 <400> 416 Met Met Ala Ala Val Pro Pro Gly Leu Glu Pro Trp Asn Arg Val Arg -50 -55 Ile Pro Lys Ala Gly Asn Arg Ser Ala Val Thr Val Gln Asn Pro Gly -40 -35 Ala Ala Leu Asp Leu Cys Ile Ala Ala Val Ile Lys Glu Cys His Leu -20 -15 -25 Val Ile Leu Ser Leu Lys Ser Gln Thr Leu Asp Ala Glu Thr Asp Val -10 -5 Leu Cys Ala Val Leu Tyr Ser Asn His Asn Arg Met Gly Arg His Lys 10 15 Pro His Leu Ala Leu Lys Gln Val Glu Gln Cys Leu Lys Arg Leu Lys 25 30 Asn Met Asn Leu Glu Gly Ser Ile Gln Asp Leu Phe Glu Leu Phe Ser Ser Lys

<210> 417
<211> 161
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -108..-1
<400> 417

Met Thr Ser Gly Gln Ala Arg Ala Ser Xaa Gln Ser Pro Gln Ala Leu -105 -100 -95 Glu Asp Ser Gly Pro Val Asn Ile Ser Val Ser Ile Thr Leu Thr Leu ~90 -85 -80 Asp Pro Leu Lys Pro Phe Gly Gly Tyr Ser Arg Asn Val Thr His Leu -65 -70 Tyr Ser Thr Ile Leu Gly His Gln Ile Gly Leu Ser Gly Arg Glu Ala -60 -55 -50 -45 His Glu Glu Ile Asn Ile Thr Phe Thr Leu Pro Thr Ala Trp Ser Ser -40 -35 Asp Asp Cys Ala Leu His Gly His Cys Glu Gln Val Val Phe Thr Ala -15 -25 -20 Cys Met Thr Leu Thr Ala Ser Pro Gly Val Phe Pro Ser Leu Tyr Ser

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- 5
His Arg Thr Val Phe Leu Thr Arg Thr Ala Thr Pro Arg Ser Gly Thr
              10 15 20
Arg Ser Ser Gln Leu Pro Glu Met Pro Thr Gln Asn Thr Pro Lys Ile
                       30
Thr Ile Leu Ser Gly Val Ile Arg Gly Pro Leu Glu Lys Ser Ile Met
Leu
<210> 418
<211> 67
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 418
Met Leu Gly Gly Asp His Arg Ala Leu Leu Leu Lys Ile Trp Leu Leu
                     -15
                                      -10
Gln Arg Pro Glu Ser Gln Glu Gly Leu Leu Pro Gly Arg Leu Val Val
                 1
                        5
Met Glu Arg Arg Val Lys Asn Asp Leu Met Ser Phe Leu Ser Thr Val
         15
                       20
Leu Leu Ser Phe His Ser Ser Asn Ala Arg Val Ser His Cys Glu Pro
   30 · 35
Leu Arg Met
  45
<210> 419
<211> 332
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -32..-1
<400> 419
Met Ile Xaa Leu Arg Asp Thr Ala Ala Ser Leu Arg Leu Glu Arg Asp
                       -25
Thr Arg Gln Leu Pro Leu Leu Thr Ser Ala Leu His Gly Leu Gln Gln
                     -10
                                      - 5
Gln His Pro Ala Phe Ser Gly Val Ala Arg Leu Ala Lys Arg Trp Val
                                10
Arg Ala Gln Leu Leu Gly Glu Gly Phe Ala Asp Glu Ser Leu Asp Leu
                             25
Val Ala Ala Ala Leu Phe Leu His Pro Glu Pro Phe Thr Pro Pro Ser
                         40
                                           45
```

Ser Pro Gln Val Gly Phe Leu Arg Phe Leu Phe Leu Val Ser Thr Phe

Asp Trp Lys Asn Asn Pro Leu Phe Val Asn Leu Asn Asn Glu Leu Thr

Val Glu Glu Gln Val Glu Ile Arg Ser Gly Phe Leu Ala Ala Arg Ala

Gln Leu Pro Val Met Val Ile Val Thr Pro Gln Xaa Arg Lys Asn Ser

105

60

75

90

55

70

85

```
Val Trp Thr Gln Asp Gly Pro Ser Ala Gln Ile Leu Gln Gln Leu Val
                    120
Val Leu Ala Ala Glu Xaa Leu Pro Met Leu Xaa Xaa Gln Leu Met Asp
                 135 140
Pro Arg Gly Pro Gly Asp Ile Arg Thr Xaa Phe Arg Pro Pro Leu Asp
             150 155
Ile Tyr Asp Val Leu Ile Arg Leu Ser Pro Arg His Ile Pro Arg His
               170 175
           165
Arg Gln Ala Val Asp Ser Pro Ala Ala Ser Phe Cys Arg Gly Leu Leu
        180 185 190
Ser Gln Pro Gly Pro Ser Ser Leu Met Pro Val Leu Gly Xaa Asp Pro
     195 200 205
Pro Gln Leu Tyr Leu Thr Gln Leu Xaa Glu Ala Phe Gly Asp Leu Ala
  210 215
                                220
Leu Phe Phe Tyr Asp Gln His Gly Gly Glu Val Ile Gly Val Leu Trp
225 230
                            235
Lys Pro Thr Ser Phe Gln Pro Gln Pro Phe Lys Ala Ser Ser Thr Lys
           245 250 255
Gly Arg Met Val Met Ser Arg Gly Glu Leu Val Met Val Pro Asn
                      265
       260
Val Glu Ala Ile Leu Glu Asp Phe Ala Val Leu Gly Glu Gly Leu Val
     275 280
Gln Thr Val Glu Ala Arg Ser Glu Arg Trp Thr Val
                 295
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<210> 421 <211> 57

-10 - 5 Arg Val Tyr His Tyr Phe Gln Trp Arg Arg Ala Gln Arg Gln Ala Ala 5 10 Glu Glu Gln Lys Xaa Ser Gly Ile Met <210> 422 <211> 85 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -17..-1 Met Lys Lys Val Leu Leu Ile Thr Ala Ile Leu Ala Val Ala Val -10 Gly Phe Pro Val Ser Gln Asp Gln Glu Arg Glu Lys Arg Ser Ile Ser Asp Ser Asp Glu Leu Ala Ser Gly Xaa Phe Val Phe Pro Tyr Pro Tyr 20 25 Pro Phe Arg Pro Leu Pro Pro Ile Pro Phe Pro Arg Phe Pro Trp Phe 40 Arg Arg Asn Phe Pro Ile Pro Ile Pro Glu Ser Ala Pro Thr Thr Pro 55 Leu Pro Ser Glu Lys 65 <210> 423 <211> 85 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -17..-1 <400> 423 Met Lys Lys Val Leu Leu Leu Ile Thr Ala Ile Leu Ala Val Ala Val -15 -10 -5 Gly Phe Pro Val Ser Gln Asp Xaa Glu Arg Glu Lys Arg Ser Ile Ser 10 Asp Ser Asp Glu Leu Ala Ser Gly Phe Phe Val Phe Pro Tyr Pro Tyr

25

Pro Phe Arg Pro Leu Pro Pro Ile Pro Phe Pro Arg Phe Pro Trp Phe 35 40 45 Arg Arg Asn Phe Pro Ile Pro Ile Pro Glu Ser Ala Pro Thr Thr Pro

55

<210> 424 <211> 69 <212> PRT <213> Homo sapiens

50

65

Leu Pro Ser Glu Lys

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<220>
<221> SIGNAL
<222> -29..-1
<400> 424
Met Thr Cys Arg Gly Ser Cys Ser Tyr Ala Thr Arg Arg Ser Pro Ser
                            -20 -15
           -25
Glu Leu Ser Leu Leu Pro Ser Ser Leu Trp Val Leu Ala Thr Ser Ser
                       - 5
 -10
Pro Thr Ile Thr Ile Ala Leu Ala Met Ala Ala Gly Asn Leu Cys Pro
             10
                           15
Leu Pro Ser Ser Xaa Arg Xaa Lys Arg Arg Trp Cys Gln Ala Xaa Gln
                         30
Gln Xaa Ala Leu Leu
<210> 425
<211> 122
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -56..-1
<400> 425
Met Val Pro Trp Pro Arg Gly Lys Val Lys Thr Ala Pro Ile Pro Ile
-55 <del>-</del>50
                        -45
Ser Arg Phe Pro Phe Leu Pro Thr His Asp Pro Pro Thr Pro Ala His
                            -30 -25
-40 -35
Trp Ser Pro Ala Ser His Gln Gln Phe Lys His Xaa Ser Pro Leu Leu
          -20 -15 -10
Thr Leu Ala Leu Leu Gly Gln Cys Ser Leu Phe Xaa Asn Leu Arg Lys
       -5 1 5
Lys Leu Ala Gly Gln Lys Ala Lys Lys Leu Pro Ser Phe Ser Ser Leu
10 15
Pro Leu Thr Leu Trp Pro Leu Thr Pro Gln Phe Ala Glu Leu Thr Thr
  30 35
Val Ala Gln Lys Lys Leu Arg Trp Ser Gly Thr Leu Gly Trp Gly Pro
                50
          45
Val Pro Ser Trp Val Gln Phe Phe Leu Gly
<210> 426
<211> 41
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -30..-1
<400> 426
Met Ala Cys Glu Thr His Gly Val Leu Val Pro Ala His Leu Ser Gly
```

Leu Ile Thr Cys Leu Leu Ala Phe Trp Val Pro Ala Ser Cys Ile Gln

-5

-25

-10

-20 -15

Arg Cys Ser Gly Ser Pro Leu Pro Leu
5 10

<210> 427 <211> 50 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -36..-1 <400> 427 Met Ala Pro His Thr Ala Ser Phe Gly Val Cys Pro Leu Leu Ser Val -35 . -30 -25 Thr Arg Val Val Ala Thr Glu His Trp Leu Phe Leu Ala Ser Leu Ser -20 - -15 -10 Gly Ile Lys Thr Tyr Gln Ser Tyr Ile Ser Val Phe Cys Lys Val Thr 1 5 Leu Ile <210> 428 <211> 136 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -18..-1 <400> 428 Met Asp Ser Leu Arg Lys Met Leu Ile Ser Val Ala Met Leu Gly Ala -15 -10 -5 Xaa Ala Gly Val Gly Tyr Ala Leu Leu Val Ile Val Thr Pro Gly Glu 10 Arg Arg Lys Gln Glu Met Leu Lys Glu Met Pro Leu Gln Asp Pro Arg 20 25 30 Ser Arg Glu Glu Ala Ala Arg Thr Gln Gln Leu Leu Leu Ala Thr Leu

35 40 45

Met Pro Gly Leu Ser Gly Val Leu

115

<210> 429 <211> 194 <212> PRT

<213> Homo sapiens

<220>

<222> -65..-1 <400> 429 Met Gln Asp Ala Pro Leu Ser Cys Leu Ser Pro Thr Lys Trp Ser Ser -60 -55 Val Ser Ser Ala Asp Ser Thr Glu Lys Ser Ala Ser Ala Ala Gly Thr -45 -40 -35 Arg Asn Leu Pro Phe Gln Phe Cys Leu Arg Gln Ala Leu Arg Met Lys -25 Ala Ala Gly Ile Leu Thr Leu Ile Gly Cys Leu Val Thr Gly Val Glu -15 -10 -5 Ser Lys Ile Tyr Thr Arg Cys Lys Leu Ala Lys Ile Phe Ser Arg Ala 5 10 Gly Leu Asp Asn Xaa Arg Gly Phe Ser Leu Gly Asn Trp Ile Cys Met 20 25 Ala Tyr Tyr Glu Ser Gly Tyr Asn Thr Thr Ala Gln Thr Val Leu Asp 40 Asp Gly Ser Ile Asp Tyr Gly Ile Phe Gln Ile Asn Ser Phe Ala Trp 55 Cys Arg Arg Gly Lys Leu Lys Glu Asn Asn His Cys His Val Ala Cys 70 75 Ser Ala Leu Xaa Thr Asp Asp Leu Thr Asp Ala Ile Ile Cys Ala Xaa 90 85 Lys Ile Val Lys Glu Thr Gln Gly Met Asn Tyr Trp Gln Gly Trp Lys 100 105 Lys His Cys Glu Gly Arg Asp Leu Ser Xaa Trp Lys Lys Gly Cys Glu 120 Val Ser

<221> SIGNAL

<210> 430 <211> 141

<212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> ~69..-1 <400> 430 Met Thr Ser Gln Pro Val Pro Asn Glu Thr Ile Ile Val Leu Pro Ser -60 Asn Val Ile Asn Phe Ser Gln Ala Glu Lys Pro Glu Pro Thr Asn Gln -45 Gly Gln Asp Ser Leu Lys Lys His Leu His Ala Glu Ile Lys Val Ile -30 -25 Gly Thr Ile Gln Ile Leu Cys Gly Met Met Val Leu Ser Leu Gly Ile -15 -10 Ile Leu Ala Ser Ala Ser Phe Ser Pro Asn Phe Thr Gln Val Thr Ser 1 5 Thr Leu Leu Asn Ser Ala Tyr Pro Phe Ile Gly Pro Phe Phe Val Xaa 20 Lys Xaa Ser Glu Glu Gly Arg Met Gly Gln Xaa Gly Glu Glu Xaa Xaa 35 Asn Ser Leu Asn Phe Pro Xaa Ala Ser Leu Leu Xaa Leu Ile Cys Gln 50 55 Xaa Gln Gly Phe Asn Gly Glu Ser Cys Ser Pro Val Gly

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<210> 431
<211> 248
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -69..-1
<400> 431
Met Thr Ser Gln Pro Val Pro Asn Glu Thr Ile Ile Val Leu Pro Ser
         -65 -60 -55
Asn Val Ile Asn Phe Ser Gln Ala Glu Lys Pro Glu Pro Thr Asn Gln
         -50
                   -45
Gly Gln Asp Ser Leu Lys Lys His Leu His Ala Glu Xaa Lys Val Ile
      -35 · -30 -25
Gly Thr Ile Gln Ile Leu Cys Gly Met Met Val Leu Ser Leu Gly Ile
                -15
                                 -10
Ile Leu Ala Ser Ala Ser Phe Ser Pro Asn Phe Thr Gln Val Thr Ser
   1 5
Thr Leu Leu Asn Ser Ala Tyr Pro Phe Ile Gly Pro Phe Phe Phe Ile
                20
       15
Ile Ser Gly Ser Leu Ser Ile Ala Thr Lys Lys Arg Leu Thr Asn Leu
Leu Val His Thr Thr Leu Val Gly Ser Ile Leu Ser Ala Leu Ser Ala
Leu Val Gly Phe Ile Xaa Leu Ser Val Lys Gln Ala Thr Leu Asn Pro
                                70 75
Ala Ser Leu Xaa Cys Glu Leu Xaa Lys Asn Asn Ile Pro Thr Xaa Xaa
                             85
Tyr Val Xaa Tyr Phe Tyr His Asp Ser Leu Tyr Thr Thr Asp Xaa Tyr
       95
                         100 105
Thr Ala Lys Ala Xaa Leu Ala Gly Thr Leu Ser Leu Met Leu Ile Cys
      110
                             120
                      115
Thr Leu Leu Glu Phe Cys Xaa Xaa Val Leu Thr Ala Val Leu Arg Trp
                  130
Lys Gln Ala Tyr Ser Asp Phe Pro Gly Ser Val Leu Phe Leu Pro Xaa
140 145
                    150 155
Ser Tyr Ile Gly Asn Ser Gly Met Ser Ser Lys Met Thr His Asp Cys
             160
                             165
Gly Tyr Glu Glu Leu Leu Thr Ser
         175
```

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<210> 432
<211> 49
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -36..-1
<400> 432
Met Gln Val Pro His Leu Arg Val Trp Thr Gln Val Xaa Asp Thr Phe
Ile Gly Tyr Arg Asn Leu Gly Phe Thr Ser Met Cys Ile Leu Phe His
```

-30

-15

1

-25

-10

Cys Leu Leu Ser Phe Gln Val Phe Lys Lys Lys Arg Lys Leu Xaa Leu 5

Phe

<210> 433 <211> 86 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -14..-1 <400> 433 Met Val Ala Leu Asn Leu Ile Leu Val Pro Cys Cys Ala Ala Trp Cys -5 -10 Asp Pro Arg Arg Ile His Ser Gln Asp Asp Val Leu Arg Ser Ser Ala 10 Ala Asp Thr Gly Ser Ala Met Gln Arg Arg Glu Ala Trp Ala Gly Trp 25 . Arg Arg Ser Gln Pro Phe Ser Val Gly Leu Pro Ser Ala Glu Arg Leu 45 Glu Asn Gln Pro Gly Lys Leu Ser Trp Arg Ser Leu Val Gly Glu Gly 55 60 His Arg Ile Cys Asp Leu 70

<210> 434 <211> 144 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -58..-1

<400> 434 Met Thr Arg Leu Cys Leu Pro Arg Pro Glu Ala Arg Glu Asp Pro Ile -55 -50 Pro Val Pro Pro Arg Gly Leu Gly Ala Gly Glu Gly Ser Gly Ser Pro -35 -30 Val Arg Pro Pro Val Ser Thr Trp Gly Pro Ser Trp Ala Gln Leu Leu -20 -15 Asp Ser Val Leu Trp Leu Gly Ala Leu Gly Leu Thr Ile Gln Ala Val -5 1 5 Phe Ser Thr Thr Gly Pro Ala Leu Leu Leu Leu Leu Val Ser Phe Leu 15 Thr Phe Asp Leu Leu His Arg Pro Ala Val Thr Leu Cys His Ser Ala Asn Phe Ser Pro Gly Ala Arg Val Arg Gly Pro Val Lys Val Leu Asp Ser Arg Arg Leu Tyr Ser Cys Lys Trp Val Gln Ser Gln Asp Asn Leu Ala Ser Arg Lys His Cys Cys Cys Cys Ser Trp Gly Trp Ala Arg Ser

<210> 435 <211> 121

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<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -16..-1
<400> 435
Met Glu Arg Leu Val Leu Thr Leu Cys Thr Leu Pro Leu Ala Val Ala
                   -10
                                  -5
Ser Ala Gly Cys Ala Thr Thr Pro Ala Arg Asn Leu Ser Cys Tyr Gln
                                10
Cys Phe Lys Val Ser Ser Trp Thr Glu Cys Pro Pro Thr Trp Cys Ser
                    25
Pro Leu Asp Gln Val Cys Ile Ser Asn Glu Val Val Val Ser Phe Ser
 35
                        40
Glu Ser Pro Pro Gly Arg Gly Xaa Val Pro Xaa Ala Gly Glu Xaa Pro
                     55
                                       60
Val Pro Pro Pro Leu Xaa Asp Leu Xaa Met Thr Pro Arg Xaa Xaa Arg
                 70
                                  75
Ala Trp Gly Pro Val Gly Pro Lys Val Pro Pro Ala Val Ser Pro Ala
              85
                             90
Leu Gly Ser Gly Glu His Pro Xaa Xaa
           100
```

<210> 436 <211> 162

145

<212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -16..-1 <400> 436 Met Glu Arg Leu Val Leu Thr Leu Cys Thr Leu Pro Leu Ala Val Ala -10 Ser Ala Gly Cys Ala Thr Thr Pro Ala Arg Asn Leu Ser Cys Tyr Gln 10 Cys Phe Lys Val Ser Ser Trp Thr Glu Cys Pro Pro Thr Trp Cys Ser 20 25 Pro Leu Asp Gln Val Cys Ile Ser Asn Glu Val Val Ser Phe Lys 40 Trp Ser Val Arg Val Leu Leu Ser Lys Arg Cys Ala Pro Arg Cys Pro 55 Asn Asp Asn Met Xaa Phe Glu Trp Ser Pro Ala Pro Met Val Gln Gly 70 Val Ile Thr Arg Arg Cys Cys Ser Trp Ala Leu Cys Asn Arg Ala Leu . 95 85 90 Thr Pro Gln Glu Gly Arg Trp Ala Leu Xaa Gly Gly Leu Leu Leu Gln 100 105 Asp Pro Ser Arg Gly Xaa Lys Thr Trp Val Arg Pro Gln Leu Gly Leu 120 Pro Leu Cys Leu Pro Xaa Ser Asn Pro Leu Cys Pro Xaa Glu Thr Gln 135 Glu Gly

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<210> 437
 <211> 110
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -20..-1
 <400> 437
 Met Xaa Leu Met Val Leu Val Phe Thr Ile Gly Leu Thr Leu Leu Leu
 -20 -15
                               -10
 Gly Xaa Gln Ala Met Pro Ala Asn Arg Leu Ser Cys Tyr Arg Lys Ile
      1
                                         10
 Leu Lys Asp His Asn Cys His Asn Leu Pro Glu Gly Val Ala Asp Leu
  15
              20
 Thr Gln Ile Asp Val Asn Val Gln Asp His Phe Trp Asp Gly Lys Gly
  30
           35
                            40
 Cys Glu Met Ile Cys Tyr Cys Asn Phe Lys Arg Ile Ala Leu Leu Pro
                        55
 45
               50
. Lys Arg Arg Phe Leu Trp Thr Lys Asp Leu Phe Arg Asp Ser Leu Gln
                     70
 Gln Ser Met Arg Ile Phe Met Tyr Ser Gly Glu His His Ser
          80
                        85
 <210> 438
 <211> 71
 <212> PRT
 <213> Homo sapiens
<220>
 <221> SIGNAL
 <222> -15..-1
 <400> 438
 Met Lys Leu Leu Thr His Asn Leu Leu Ser Ser His Val Arg Gly Val
 -15 -10 -5 1
 Gly Ser Arg Gly Phe Pro Leu Arg Leu Gln Ala Thr Glu Val Arg Ile
                          10 15
 Cys Pro Val Glu Phe Asn Pro Asn Phe Val Ala Arg Met Ile Pro Lys
      20 25
                            30
 Val Glu Trp Ser Ala Phe Leu Glu Ala Xaa Asp Asn Leu Arg Leu Ile
 Gln Val Pro Arg Arg Ala Gly
 <210> 439
 <211> 99
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -24..-1
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<400> 439
Met Lys Ser Ala Lys Leu Gly Phe Leu Leu Arg Phe Phe Ile Phe Cys
-20 -15 -10

```
<210> 440
 <211> 169
 <212> PRT
 <213> Homo sapiens
. <220>
 <221> SIGNAL
 <222> -25..-1
 <400> 440
 Met Arg Lys Pro Ala Ala Gly Phe Leu Pro Ser Leu Leu Lys Val Leu
      -20 -15 -10
 Leu Leu Pro Leu Ala Pro Ala Ala Ala Gln Asp Ser Thr Gln Ala Ser
                -5
                                  1
 Thr Pro Gly Ser Pro Leu Ser Pro Thr Glu Tyr Gln Arg Phe Phe Ala
        10
              15
 Leu Leu Thr Pro Thr Trp Lys Ala Glu Thr Thr Cys Arg Leu Arg Ala
                    30
 Thr His Gly Cys Arg Asn Pro Thr Leu Val Gln Leu Asp Gln Tyr Glu
                   45
                                     50 55
 Asn His Gly Leu Val Pro Asp Gly Ala Val Cys Ser Asn Leu Pro Tyr
                                  65
 Ala Ser Trp Phe Glu Ser Phe Cys Gln Phe Thr His Tyr Arg Cys Ser
                              80
 Asn His Val Tyr Tyr Ala Lys Arg Val Leu Cys Ser Gln Pro Val Ser
                          95
 Ile Leu Ser Pro Asn Thr Leu Lys Glu Ile Glu Xaa Ser Ala Glu Val
                      110
                                        115
 Ser Pro Thr Thr Asp Asp Leu Pro His Leu Thr Pro Leu His Ser Asp
                  125
                                    130
 Arg Thr Pro Asp Leu Pro Ala Leu Ala
```

```
Ala Asp Cys Gly Thr Ile Leu Leu Gln Asp Lys Gln Arg Lys Ile Tyr
           -55
                             -50
Cys Val Ala Cys Gln Glu Leu Asp Ser Asp Val Asp Lys Asp Asn Pro
                  -35 -30
      -40
Ala Leu Asn Ala Gln Ala Ala Leu Ser Gln Ala Arg Glu His Gln Leu
   . -25 -20 -15
Ala Ser Ala Ser Glu Leu Pro Leu Gly Ser Arg Pro Ala Pro Gln Pro
   -10 -5
Pro Val Pro Arg Pro Glu His Cys Glu Gly Ala Ala Ala Gly Leu Lys
       10 15 20
Ala Ala Gln Gly Pro Pro Ala Pro Ala Val Pro Pro Asn Thr Xaa Val
           25 30 35
Met Ala Cys Thr Gln Thr Ala Leu Leu Gln Lys Leu Thr Trp Ala Ser
       40 45
Ala Glu Leu Gly Ser Xaa Thr Ser Xaa Gly Lys Xaa Ala Ser Ser Cys
                 60
                         65
Val Ala Leu Ser Ala His Val Arg Arg Pro Cys Ala Ala Cys Ser Ser
 70 75
Tyr Ser Thr Lys Arg Ser Pro
```

<210> 442 <211> 70 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -15..-1

Met Ile Leu Cys Phe Leu Leu Pro His His Arg Leu Gln Glu Ala Arg
-15 -10 -5 -5 -5 1
Gln Ile Gln Val Leu Lys Met Leu Pro Arg Glu Lys Leu Arg Arg Arg
5 10 -10 - 15 - 15
Glu Glu Arg Lys Gln Ile Asn Gly Lys Lys Xaa Arg Thr Lys Tyr Glu
20 - 25 - 30

Thr Pro Arg Lys Xaa Xaa Gly Lys Lys Gly Gly Asn Xaa Xaa Xaa Xaa 35 40 45

Xaa Leu Ser Lys Arg Asp 50 55

<210> 443 <211> 381 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -33..-1

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Lys Met Ala Thr Val Lys Ser Glu Leu Ile Glu Arg Phe Thr Ser Glu
                                  25
Lys Pro Val His His Ser Lys Val Ser Ile Ile Gly Thr Gly Ser Val
                              40
Gly Met Ala Cys Ala Ile Ser Ile Leu Leu Lys Gly Leu Ser Asp Glu
                         55
Leu Ala Leu Val Asp Leu Asp Glu Xaa Lys Leu Lys Gly Glu Thr Met
                      70
Asp Leu Gln His Gly Ser Pro Phe Thr Lys Met Pro Asn Ile Val Cys
                  85
                           90
Ser Lys Xaa Tyr Phe Val Thr Ala Asn Ser Asn Leu Val Ile Ile Thr
              100
                                 105 110
Ala Gly Ala Arg Gln Xaa Lys Gly Glu Thr Arg Leu Asn Leu Xaa Gln
                             120
           115
                                                125
Arg Asn Val Ala Ile Phe Lys Leu Met Ile Ser Ser Ile Val Gln Tyr
                                   140
                         135
Ser Pro His Cys Lys Leu Ile Ile Val Ser Asn Pro Val Asp Ile Leu
                      150
                                        155
Thr Tyr Val Ala Trp Lys Leu Ser Ala Phe Pro Lys Asn Arg Ile Ile
                   165
                                     170
Gly Ser Gly Cys Asn Leu Ile Xaa Ala Arg Phe Arg Phe Leu Ile Gly
                                  185
Gln Lys Leu Gly Ile His Ser Glu Ser Cys His Gly Trp Ile Leu Gly
                              200
Glu His Gly Asp Ser Ser Val Pro Val Trp Ser Gly Val Asn Ile Ala
       210
                           215
Gly Val Pro Leu Lys Asp Leu Asn Ser Asp Ile Gly Thr Asp Lys Asp
                       230
                                          235
Pro Glu Gln Trp Lys Asn Val His Lys Glu Val Thr Ala Thr Ala Tyr
                   245
                                      250
Glu Ile Ile Lys Met Lys Gly Tyr Thr Ser Trp Ala Ile Gly Leu Ser
               260
                                  265
Val Ala Asp Leu Thr Glu Ser Ile Leu Lys Asn Leu Arg Arg Ile His
           275
                              280
Pro Val Ser Thr Ile Thr Lys Gly Leu Tyr Gly Ile Xaa Glu Glu Val
                         295
Phe Leu Ser Ile Pro Cys Ile Leu Gly Glu Asn Gly Ile Thr Asn Leu
                       310
                                          315
Ile Lys Ile Lys Leu Thr Pro Glu Glu Glu Ala His Leu Lys Lys Ser
                  325
                                     330
Ala Lys Thr Leu Trp Glu Ile Gln Asn Lys Leu Lys Leu
               340
```

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<210> 445
<211> 50
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 445
Met Val Leu Thr Thr Leu Pro Leu Pro Ser Ala Asn Ser Pro Val Asn
                            - 25
   -35 -30
Met Pro Thr Thr Gly Pro Asn Ser Leu Ser Tyr Ala Ser Ser Ala Leu
 -20 -15 -10
Ser Pro Cys Leu Thr Ala Pro Lys Ser Pro Arg Leu Ala Met Met Pro
              1
                           5
Asp Asn
<210> 446
<211> 51
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1
<400> 446
Met Thr Pro Trp Cys Leu Ala Cys Leu Gly Arg Arg Pro Leu Ala Ser
                           -15
                  -20
Leu Gln Trp Ser Leu Thr Leu Ala Trp Cys Gly Ser Gly Ser His Trp
               - 5
                                1
Thr Glu Arg Pro Xaa Gln Xaa Ser Pro Trp Xaa Ser Leu Ser Ala Thr
Thr Arg Gly
     25
<210> 447
<211> 242
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -30..-1
<400> 447
Met Gly Glu Ala Ser Pro Pro Ala Pro Ala Arg Arg His Leu Leu Val
-30 -25 -20
Leu Leu Leu Leu Ser Thr Leu Val Ile Pro Ser Ala Ala Ala Pro
              -10
                            -5
Ile His Asp Ala Asp Ala Gln Glu Ser Ser Leu Gly Leu Thr Gly Leu
     5
                      10
Gln Ser Leu Leu Gln Gly Phe Ser Arg Leu Phe Leu Lys Gly Asn Leu
                   25 30
Leu Arg Gly Ile Asp Ser Leu Phe Ser Ala Pro Met Asp Phe Arg Gly
```

```
40
Leu Pro Gly Asn Tyr His Lys Glu Glu Asn Gln Glu His Gln Leu Gly
                                 60
Asn Asn Thr Leu Ser Ser His Leu Gln Ile Asp Lys Met Thr Asp Asn
Lys Thr Gly Glu Val Leu Ile Ser Glu Asn Val Val Ala Ser Ile Gln
Pro Xaa Glu Gly Xaa Phe Glu Gly Asp Leu Lys Val Pro Arg Met Glu
                      105
                                        110
Glu Lys Glu Ala Leu Val Pro Xaa Gln Lys Ala Thr Asp Ser Phe His
               120
                                    125
Thr Glu Leu His Pro Arg Val Ala Phe Trp Ile Ile Lys Leu Pro Arg
             135
                                 140
Arg Arg Ser His Gln Asp Ala Leu Glu Gly Gly His Trp Leu Xaa Glu
          150
                             155
Lys Arg His Arg Leu Gln Ala Ile Arg Asp Gly Leu Arg Lys Gly Thr
      165 . 170
His Lys Asp Xaa Leu Xaa Xaa Gly Thr Glu Ser Ser Ser His Ser Arg
          185
Leu Ser Pro Arg Lys Xaa His Leu Leu Tyr Ile Leu Xaa Pro Ser Arg
195 200
                                   205
Gln Leu
```

<210> 448 <211> 154 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -60..-1

<400> 448

Met Gly Ser Lys Cys Cys Lys Gly Gly Pro Asp Glu Asp Ala Val Glu -50 -55 Arg Gln Arg Arg Gln Lys Leu Leu Leu Ala Gln Leu His His Arg Lys -40 -35 Arg Val Lys Ala Ala Gly Gln Ile Gln Ala Trp Trp Arg Gly Val Leu -20 Val Arg Arg Thr Leu Leu Val Ala Ala Leu Arg Ala Trp Met Ile Gln -5 Cys Trp Trp Arg Thr Leu Val Gln Arg Arg Ile Arg Gln Arg Arg Gln 10 15 Ala Leu Leu Gly Val Tyr Val Ile Gln Glu Gln Ala Ala Val Lys Leu 30 Gln Ser Cys Ile Arg Met Trp Gln Cys Arg Gln Cys Tyr Arg Gln Met 45 Cys Asn Ala Leu Cys Leu Phe Gln Val Pro Lys Ser Ser Leu Ala Phe 60 Gln Thr Asp Gly Phe Leu Gln Val Gln Tyr Ala Ile Pro Ser Lys Gln 75 Pro Glu Phe His Ile Glu Ile Leu Ser Ile

<210> 449 <211> 89 <212> PRT <213> Homo sapiens

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<220>
<221> SIGNAL
<222> -61..-1
<400> 449
Met Asn Ala Ala Ile Asn Thr Gly Pro Ala Pro Ala Val Thr Lys Thr
          -55
                         -50
Glu Thr Glu Val Gln Asn Pro Asp Val Leu Trp Asp Leu Asp Ile Pro
              -40 -35
Glu Ala Arg Ser His Ala Asp Gln Asp Ser Asn Pro Lys Ala Glu Ala
            -25 -20 -15
Leu Leu Pro Cys Asn Leu His Cys Ser Trp Leu His Ser Ser Pro Arg
 -10 -5 1
Pro Asp Pro His Ser His Phe Pro Ser Xaa Arg Arg Cys Pro Leu Pro
5 10
                            15
His Pro Cys Ala Thr Tyr Pro Pro Xaa
      25
<210> 450
<211> 73
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1
Met Arg Met Ser Leu Ala Gln Arg Val Leu Leu Thr Trp Leu Phe Thr
-25 -20
Leu Leu Phe Leu Ile Met Leu Val Leu Lys Leu Asp Glu Lys Ala Pro
             - 5
Trp Asn Trp Phe Leu Ile Phe Ile Pro Val Trp Ile Phe Asp Thr Ile
                       15
Leu Leu Val Leu Leu Ile Val Lys Met Ala Gly Arg Cys Lys Ser Gly
   25 30
Phe Asp Leu Asp Met Asp His Thr Ile
  40
<210> 451
<211> 54
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -34..-1
<400> 451
Met Ile Pro Leu Ile Ser His Leu Ala Glu Ala Ala Pro Pro Thr Ser
       -30 -25 -20
Trp Ser Leu Ile Ser Ser Val Leu Asn Val Gly His Leu Leu Phe Ser
      -15 -10 -5
Ser Ala Cys Ser Val Ser Leu Glu Ala Leu Ser Thr Arg Asn Ile Lys
   1 5
                          10
```

Ala Ile Ile Leu Met Lys

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<210> 452

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<211> 121
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -38..-1
<400> 452
Met Glu Ser Pro Gln Leu His Cys Ile Leu Asn Ser Asn Ser Val Ala
                  -30
Cys Ser Phe Ala Val Gly Ala Gly Phe Leu Ala Phe Leu Ser Cys Leu
                         -15
Ala Phe Leu Val Leu Asp Thr Gln Glu Thr Arg Ile Ala Gly Thr Arg
                     1
Phe Lys Thr Ala Phe Gln Leu Leu Asp Phe Ile Leu Ala Val Leu Trp
                      20
Ala Val Val Trp Phe Met Gly Phe Cys Phe Leu Ala Asn Gln Trp Gln
                         35
His Ser Pro Pro Lys Glu Xaa Leu Leu Gly Ser Ser Ser Ala Gln Ala
            50
                                     55
Ala Ile Gly Xaa His Leu Leu His Pro Cys Leu Asp Ile Pro Xaa
                  65
Leu Pro Gly Xaa Pro Gly Pro Pro Lys
     80
<210> 453
<211> 166
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 453
Met Ser Thr Val Gly Leu Phe His Phe Pro Thr Pro Leu Thr Arg Ile
                         -30
Cys Pro Ala Pro Trp Gly Leu Arg Leu Trp Glu Lys Leu Thr Leu Leu
                     -15
                                      -10
Ser Pro Gly Ile Ala Val Thr Pro Val Gln Met Ala Gly Lys Lys Asp
               1
Tyr Pro Ala Leu Leu Ser Leu Asp Glu AsngGlu Leu Glu Glu Gln Phe
           15
                             20
Val Lys Gly His Gly Pro Gly Gly Gln Ala Thr Asn Lys Thr Ser Asn
                         35
Cys Val Val Leu Lys Xaa Ile Pro Ser Gly Ile Val Val Lys Cys His
                      50
Gln Thr Arg Ser Val Asp Gln Asn Arg Lys Leu Ala Arg Lys Ile Leu
                 65
                                     70
Gln Glu Lys Val Xaa Val Phe Tyr Asn Gly Glu Asn Ser Pro Val His
              80
                                 85
Lys Glu Lys Arg Glu Ala Ala Lys Lys Lys Gln Glu Arg Lys Lys Arg
                           100
Ala Lys Glu Thr Leu Glu Lys Lys Xaa Leu Leu Lys Xaa Leu Trp Glu
                          115
```

Ser Ser Lys Lys Val His 125

<210> 454 <211> 180 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -26..-1 <400> 454 Met Gly Ile Gln Thr Ser Pro Val Leu Leu Ala Ser Leu Gly Val Gly -25 -20 -15 Leu Val Thr Leu Leu Gly Leu Ala Val Gly Ser Tyr Leu Val Arg Arg -10 --5 1 Ser Arg Arg Pro Gln Val Thr Leu Leu Asp Pro Asn Glu Lys Tyr Leu 15 20 10 Leu Arg Leu Leu Asp Lys Thr Thr Val Ser His Asn Thr Lys Arg Phe 35 30 Arg Phe Ala Leu Pro Thr Ala His His Thr Leu Gly Leu Pro Val Gly 45 Lys His Ile Tyr Leu Ser Thr Arg Ile Asp Gly Ser Leu Val Ile Arg 55 60 65 Pro Tyr Thr Pro Val Thr Ser Asp Glu Asp Gln Gly Tyr Val Asp Leu 75 80 Val Xaa Lys Val Tyr Leu Lys Gly Val His Pro Lys Phe Pro Glu Gly 95 Gly Lys Met Ser Xaa Tyr Leu Asp Xaa Leu Lys Val Gly Asp Xaa Val 110 115 Glu Phe Xaa Gly Pro Ser Gly Leu Leu Thr Tyr Thr Gly Lys Gly His 125 Phe Asn Ile Gln Pro Asn Lys Asn Leu His Gln Asn Pro Glu Trp Arg 140 145 Arg Asn Trp Glu

<210> 455
<211> 91
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -64..-1
<400> 455
Met Thr Pro Arg Ile

<210> 457

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<210> 456
<211> 257
<212> PRT
<213> Homo sapiens
<220>
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<222> -23..-1
<400> 456
Met Arg Arg Ile Ser Leu Thr Ser Ser Pro Val Arg Leu Leu Xaa
                            -15
Leu Leu Leu Leu Ile Ala Leu Glu Ile Met Val Gly Gly His Ser
   - 5
                        1
Leu Cys Phe Asn Phe Thr Ile Lys Ser Leu Ser Arg Pro Gly Gln Pro
Trp Cys Glu Ala His Val Phe Leu Asn Lys Asn Leu Phe Leu Gln Tyr
             30
                         35
Asn Ser Asp Asn Asn Met Val Lys Pro Leu Gly Leu Leu Gly Lys Lys
                            50
Val Tyr Ala Thr Ser Thr Trp Gly Glu Leu Thr Gln Thr Leu Gly Glu
                        65
Val Gly Arg Asp Leu Arg Met Leu Leu Cys Asp Ile Lys Pro Gln Ile
                     80
Lys Thr Ser Asp Pro Ser Thr Leu Gln Val Xaa Xaa Phe Cys Gln Arg
               95
                                   100
Glu Ala Glu Arg Cys Thr Gly Ala Ser Trp Gln Phe Ala Thr Asn Gly
              110 115
Glu Lys Ser Leu Leu Phe Asp Ala Met Asn Met Thr Trp Thr Val Ile
          125
                            130
Asn His Glu Ala Ser Xaa Ile Lys Glu Thr Trp Lys Lys Asp Arg Xaa
                         145
Leu Glu Xaa Tyr Phe Arg Lys Leu Ser Lys Gly Asp Cys Asp His Trp
                     160
                                       165
Leu Arg Glu Phe Leu Gly His Trp Glu Ala Met Pro Xaa Pro Xaa Val
                 175
                                   180
Ser Pro Xaa Asn Ala Ser Xaa Ile His Trp Ser Ser Ser Xaa Leu Pro
              190
                               195
Xaa Xaa Trp Ile Ile Leu Gly Ala Phe Ile Leu Leu Xaa Leu Met Gly
                          210
Ile Val Leu Ile Cys Val Trp Trp Gln Asn Gly Xaa Xaa Ser Thr Xaa
                        225
Xaa
```

Cys Ser Gly Gln Gln Pro Phe Pro Phe Gly Ala Ser Asn Ile Pro -40 -35 Leu Leu Cly Arg Ser Arg Lys Val Ala Arg Gly Ala Pro Val Leu -20 -25 Trp Pro Phe Leu Thr Trp Ile Asn Pro Ala Leu Ser Ile Cys Asp Pro - 5 Leu Gly Ser Cys Gly Trp Xaa Cys His Thr Ala Gln Val Pro Ala Pro 15 10 Leu Gln Leu Pro Thr Ala Cys Pro Pro Leu Pro His Gly Thr Arg Ala 30 Val Gly Pro Thr Pro Gly Leu Leu Pro Glu Ala Ala Pro Xaa Thr 45 Xaa Gly Ala Leu Ser Ser Arg Ser Arg His Trp Ser Cys Ser Ile Val 60 Xaa Cys Leu His Leu His Xaa Leu Leu Ser Val Glu Thr Arg Xaa Phe 75 Xaa Lys His Leu Leu Val Leu Val Ala Val Ala His Ser Val Leu 95 Glu Pro Pro Ala Leu Val Pro Asn Val Gln Cys Glu Met Cys Thr His 110 Ser Gly Pro Arg Asp Leu Glu Ala Ala Val Val Ser Pro Ala Pro Trp 120 125 Glu

<210> 458

<211> 107

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -28..-1

<400> 458

Met Val Leu Thr Leu Gly Glu Ser Trp Pro Val Leu Val Gly Arg Arg
-25 -20 -15

Phe Leu Ser Leu Ser Ala Ala Asp Gly Ser Asp Gly Ser His Asp Ser
-10 -5

Trp Asp Val Glu Arg Val Ala Glu Trp Pro Trp Leu Ser Gly Thr Ile 5 10 15 20

Arg Ala Val Ser His Thr Asp Val Thr Lys Lys Asp Leu Lys Val Cys

Val Glu Phe Xaa Gly Glu Ser Trp Arg Lys Arg Arg Trp Ile Glu Val

Tyr Ser Leu Leu Arg Lys Ala Phe Leu Val Lys His Asn Leu Val Leu
55 60

Ala Glu Arg Lys Ser Pro Glu Ile Ser Trp Gly

<210> 459

<211> 121

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -13..-1

<400> 459 Met Leu Val Leu Arg Ser Ala Leu Thr Arg Ala Leu Ala Ser Arg Thr -10 -5 . 1 Leu Ala Pro Gln Met Cys Ser Ser Phe Ala Thr Gly Pro Arg Gln Tyr 10 Asp Gly Ile Phe Tyr Glu Phe Arg Ser Tyr Tyr Leu Lys Pro Ser Lys Met Asn Glu Phe Leu Glu Asn Phe Glu Lys Asn Ala Gln Leu Arg Thr 40 45 Ala His Ser Glu Leu Val Gly Tyr Trp Ser Val Xaa Phe Gly Gly Arg 60 65 Met Xaa Thr Val Phe His Ile Trp Lys Tyr Asp Asn Phe Ala His Arg 80 75 Thr Glu Phe Gln Lys Ala Leu Ala Lys Asp Lys Glu Trp Gln Glu Gln 90 Phe Leu Ile Pro Asn Leu Ala Leu Asn 100 . 105

<210> 461 <211> 109 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -13..-1

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<400> 461

Met Cys Leu Leu Thr Ala Leu Val Thr Gln Val Ile Ser Leu Arg Lys -10 -5 Asn Ala Glu Arg Thr Cys Leu Cys Lys Arg Arg Trp Pro Trp Xaa Pro 10 Ser Pro Arg Ile Tyr Cys Ser Ser Thr Pro Cys Asp Ser Lys Phe Pro 25 30 Thr Val Tyr Ser Ser Ala Pro Phe His Ala Pro Leu Pro Val Gln Asn 40 45 Ser Leu Trp Gly His Pro Leu His Gly Cys Ser Trp Gln Cys His His 55 60 **6**5 Pro Gln Gly Gln Asn Leu Gln Pro Ala Ser Leu Xaa Thr His Leu Ser 70 75 80 Lys Pro Lys Arg His Phe Xaa Lys Lys Xaa Cys Gln Ala

85 90 95

<210> 462 <211> 143 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -41..-1

<400> 462 Met Ala Thr Ala Thr Glu Gln Trp Val Leu Val Glu Met Val Gln Ala -35 -30 Leu Tyr Glu Ala Pro Ala Tyr His Leu Ile Leu Glu Gly Ile Leu Ile -20 -15 Leu Trp Ile Ile Arg Leu Leu Phe Ser Lys Thr Tyr Lys Leu Gln Glu 1 Arg Ser Asp Leu Thr Val Lys Glu Lys Glu Glu Leu Ile Glu Glu Trp 15 Gln Pro Glu Pro Leu Val Pro Pro Val Pro Lys Asp His Pro Ala Leu 30 Asn Tyr Asn Ile Val Ser Gly Pro Pro Ser His Lys Thr Val Val Asn 50 Gly Lys Glu Cys Ile Asn Phe Ala Ser Phe Asn Phe Leu Gly Leu Leu 65 Asp Asn Pro Arg Val Lys Ala Ala Ala Leu Ala Ser Leu Lys Lys Tyr 80 Gly Val Gly Thr Cys Gly Pro Cys Gly Phe Tyr Gly Thr Phe Glu

· 95

<210> 463 <211> 232 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -30..-1

<400> 463 Met Ala Ala Thr Ser Gly Thr Asp Glu Pro Val Ser Gly Glu Leu Val -25 -20 Ser Val Ala His Ala Leu Ser Leu Pro Ala Glu Ser Tyr Gly Asn Xaa -10 -5 Xaa Asp Ile Glu Met Ala Trp Ala Met Arg Ala Met Gln His Ala Glu 10 Val Tyr Tyr Lys Leu Ile Ser Ser Val Asp Pro Gln Phe Leu Lys Leu Thr Lys Val Asp Asp Gln Ile Tyr Ser Glu Phe Arg Lys Asn Phe Glu 40 Thr Leu Arg Ile Asp Val Leu Xaa Pro Glu Xaa Leu Lys Ser Glu Ser 60 Ala Lys Glu Pro Pro Gly Tyr Asn Ser Leu Pro Leu Lys Leu Leu Gly Thr Gly Lys Ala Ile Thr Lys Leu Phe Ile Ser Val Phe Arg Thr Lys 90 Lys Glu Arg Lys Glu Ser Thr Met Glu Glu Lys Lys Glu Leu Thr Val

```
100
                   105
                                     110
Glu Lys Lys Arg Thr Pro Arg Met Glu Glu Arg Lys Glu Leu Ile Val
115 120 125 130
Glu Lys Lys Lys Arg Lys Glu Ser Thr Glu Lys Thr Lys Leu Thr Lys
            135 140 145
Glu Glu Lys Lys Gly Lys Lys Leu Thr Lys Lys Ser Thr Lys Val Val
                 155
         150
Lys Lys Leu Cys Lys Val Tyr Arg Glu Gln His Ser Arg Ser Tyr Asp
      165 170
                             175
Ser Ile Glu Thr Thr Ser Thr Thr Val Leu Leu Ala Gln Thr Pro Leu
  180 185
Val Lys Cys Lys Phe Leu Tyr Asn
               200
<210> 464
<211> 61
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 464
Met Thr Phe Arq His Gln Asp Asn Ser Leu Met Phe Phe Ser Met Met
                   -15
                               -10
Ala Thr Cys Thr Ser Asn Val Gly Phe Thr His Thr Thr Met Asn Cys
                           5
               1
Ser Leu Thr Ser Pro Val Asp Phe Lys Asp Leu Leu Arg Val Leu Leu
   15
                 20
Ile Lys Phe Gly Tyr Asp Arg Lys Ser Thr Ile Lys Ser
                       35
<210> 465
<211> 34
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 465
Met Phe Leu Lys Ser Gly Ala Gly Leu Ser Ser Cys Leu Leu Pro Leu
             -15
                              -10
Cys Trp Leu Glu Arg Lys Asp His Gly Arg Arg Pro Ser Xaa His Pro
               5
Gly Arg
   15
<210> 466
<211> 215
<212> PRT
<213> Homo sapiens
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<220>

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<221> SIGNAL
<222> -54..-1
<400> 466
Met Asn Xaa Tyr Ala Ser Pro Phe Asn Xaa Gln Leu Xaa Tyr Leu Xaa
         -50
               -45 -40
Leu Ser Arg Phe Glu Cys Val His Arg Asp Gly Arg Val Ile Thr Leu
               -30
Ser Tyr Gln Glu Gln Glu Leu Gln Asp Phe Leu Leu Ser Gln Met Ser
-20 -15
                         -10
Gln His Gln Val His Ala Val Gln Gln Leu Ala Lys Val Met Gly Trp
 -5 1 5
Gln Val Leu Ser Phe Ser Asn His Val Gly Leu Gly Pro Ile Glu Ser
     15 20
Xaa Gly Asn Ala Ser Ala Ile Thr Val Ala Pro Gln Val Val Thr Met
      30 35
Leu Phe Gln Phe Val Met Asp Leu Lys Val Ala Ala Arg Leu Trp Phe
                   50
                       55
Ser Phe Leu Val Thr Asn Val Lys Thr Phe Gln Lys Val Met Phe Tyr
                   70
 60 65
Lys Ile Thr Asn Gly Val Ile Phe Val Gly His Ser Lys Lys Phe Ser
75 80
                            85
Gly Ile Lys Trp Lys Val Xaa Ile Leu Phe Ile Lys Trp Xaa Cys Leu
     95 100 105
Cys Leu His Leu Ala Leu Val Tyr Tyr Asp Phe Phe Gln Met Phe Pro
       110 115 120
Lys Xaa Val Ser Xaa Asn Phe Asp Leu Lys Cys Leu Gln Ile Asn Tyr
                   130 135
Lys His Lys Glu Glu Ile Thr Ser Lys Arg Val Leu Phe Leu Lys Ile
140 145
                        150
Ile Ile Arg Lys Cys Phe Ile
             160
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<210> 468 <211> 85 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -24..-1 <400> 468 WO 99/31236 -335- PCT/IB98/02122 -

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        Met
        Cys
        Ser
        His
        Ala
        Ser
        Met
        Ser
        Phe
        His
        Thr
        Leu
        Phe
        His
        Leu
        Phe
        Leu
        Leu
        Phe
        Ass
        Leu
        Phe
        Phe</th
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20 25 Pro Asn Phe 35

<210> 470 <211> 67 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -43..-1 <400> 470

<210> 471 <211> 63 <212> PRT <213> Homo sapiens

<222> -71..-1

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<220>
<221> SIGNAL
<222> -15..-1
<400> 471
Met Gly Ile Leu Ser Thr Val Thr Ala Leu Thr Phe Ala Arg Ala Leu
-15 -10 -5
Asp Gly Cys Arg Asn Gly Ile Ala His Pro Ala Ser Glu Lys His Arg
      5
                  10 15
Leu Glu Lys Cys Arg Glu Leu Glu Ser Ser His Ser Ala Pro Gly Ser
           25
                           30
Thr Gln His Arg Arg Lys Thr Thr Arg Arg Asn Tyr Ser Ser Ala
               40
                          45
<210> 472
<211> 179
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -58..-1
<400> 472
Met Ser Thr Gly Gln Leu Tyr Arg Met Glu Asp Ile Gly Arg Phe His
      -55 -50 -45
Ser Gln Gln Pro Gly Ser Leu Thr Pro Ser Ser Pro Thr Val Gly Glu
                    -35
Ile Ile Tyr Asn Asn Thr Arg Asn Thr Leu Gly Trp Ile Gly Gly Ile
 -25 -20 -15
Leu Met Gly Ser Phe Gln Gly Thr Ile Ala Gly Gln Gly Thr Gly Ala
-10 -5
                   1 5
Thr Ser Ile Ser Glu Leu Cys Lys Gly Gln Glu Leu Glu Pro Ser Gly
      10 15
Ala Gly Leu Thr Val Ala Pro Pro Gln Ala Val Ser Leu Gln Gly Ile
25 30
Tyr Thr Leu Pro Trp Leu Leu Gln Leu Phe His Ser Thr Ala Leu Xaa
 40 45
Xaa Xaa Gln Gln Pro Asn Gly Ser Leu Ser Leu Asn Ile Ser Ser Ser
55 60
                             65 70
His Ala Pro Xaa Pro Xaa Thr Cys Thr Leu Glu Pro Gly Val Asp Pro
           75
              80
Thr Arg Xaa Val Cys Ile Asn Pro His Pro Pro Pro Pro Ile Leu Lys
   90 95 100
Xaa Pro Leu Ser Pro Tyr Pro Lys Pro Gln Leu Gly Thr His Ala Gly
 105 110
Gln Val Asn
  120
<210> 473
<211> 238
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
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<400> 473
Met Xaa Xaa Phe Thr Asp Pro Ser Ser Val Asn Glu Lys Lys Arg Arg
                   -65
Glu Arg Glu Glu Arg Gln Asn Ile Val Leu Trp Arg Gln Pro Leu Ile
                -50
                                 -45
Thr Leu Gln Tyr Phe Ser Leu Glu Ile Leu Val Ile Leu Lys Glu Trp
                              -30
Thr Ser Lys Leu Trp His Arg Gln Ser Ile Val Val Ser Phe Leu Leu
                           -15
Leu Leu Ala Gly Leu Ile Ala Thr Tyr Tyr Val Glu Gly Val His Gln
                       1
Gln Tyr Val Gln Arg Ile Glu Lys Gln Phe Leu Leu Tyr Ala Tyr Trp
          15
                               20
Ile Gly Leu Gly Ile Leu Ser Ser Val Gly Leu Gly Thr Gly Leu His
            30
                              35
Thr Phe Leu Leu Tyr Leu Gly Pro His Ile Ala Ser Val Thr Leu Ala
                          50
Ala Tyr Glu Cys Asn Ser Val Asn Phe Pro Glu Pro Pro Tyr Pro Asp
                       65
Gln Ile Ile Cys Pro Asp Glu Glu Gly Thr Glu Gly Thr Ile Ser Leu
                   80
Trp Ser Ile Ile Ser Lys Val Arg Ile Glu Ala Cys Met Trp Gly Ile
         95 100
Gly Thr Ala Ile Gly Glu Leu Pro Pro Tyr Phe Met Ala Arg Ala Ala
           110 115 120
Arg Leu Ser Gly Ala Glu Pro Asp Asp Glu Glu Tyr Gln Glu Phe Glu
         125
                          130 135
Glu Met Leu Glu His Ala Glu Ser Ala Gln Val Arg Thr Val Gly Ile
   140 145
Glu Asn Arg Thr Leu Tyr Phe Phe Leu Lys Arg Leu Leu Arg
                   160
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<210> 474 <211> 178 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<400> 474

<222> -37..-1

 Met
 Glu
 Arg
 Gln
 Ser
 Arg
 Val
 Met
 Ser
 Glu
 Lys
 Asp
 Glu
 Tyr
 Gln
 Phe

 Gln
 His
 Gln
 Gly
 Ala
 Val
 Glu
 Leu
 Val
 Phe
 Asn
 Phe
 Leu
 Leu
 Ile
 Leu
 Ile
 Arg
 Phe
 Arg

```
100
          95
His Ala Gly Tyr Ser Leu Lys Lys Arg His Phe Phe Gln Asn Leu Gly .
 110 115 120
Ser Ile Leu Thr Tyr Ala Phe Leu Gly Thr Ala Ile Ser Cys Ile Val
           130
Ile Gly
140
<210> 475
<211> 96
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 475
Met Ser Met Gln Phe Leu Phe Lys Met Val Ala Leu Cys Cys Cys Leu
              -15
Trp Lys Ile Ser Gly Cys Glu Glu Val Pro Leu Thr Tyr Asn Leu Leu
Lys Cys Leu Leu Asp Lys Ala His Cys Val Leu Leu Thr Pro Cys Gly
                     20
Tyr Ile Phe Ser Leu Ile Ser Pro Glu Ile Leu Lys Leu Thr Leu Ile
                        35
Thr Leu Xaa Ile Leu Leu Ile Leu Lys Asn Leu His Leu Leu Trp Leu
 45 50
Thr Val Ser Ser Xaa Cys Val His Arg Ser Ser Ala Arg Lys Glu Lys
   65 70
<210> 476
<211> 41
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -24..-1
<400> 476
Met His Thr Phe Ala Asn Asp Arg Gly Leu Tyr Arg Ile Leu Leu Leu
             -20 -15
His Phe Tyr Cys Leu Leu Arg Ser Ser Glu Tyr Ile Leu Gly Tyr Lys
        -5
Val Leu Gly Val Phe Phe Pro Ile Leu
                  15
<210> 477
<211> 113
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
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<222> -27..-1

WO 99/31236 -339-PCT/IB98/02122 -

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<400> 477
Met Arg Xaa Lys Trp Lys Met Gly Gly Met Lys Tyr Ile Phe Ser Leu
                           -20
Leu Phe Phe Leu Leu Glu Gly Gly Xaa Thr Glu Gln Val Xaa His
                       -5
Ser Glu Thr Tyr Cys Met Phe Gln Asp Lys Lys Tyr Arg Val Gly Glu
              10
                                  15
Arg Trp His Pro Tyr Leu Glu Pro Tyr Gly Leu Val Tyr Cys Val Asn
                              30
Cys Ile Cys Ser Glu Asn Gly Asn Val Leu Cys Ser Arg Val Arg Cys
                          45
Pro Asn Val His Cys Leu Ser Pro Val His Ile Pro His Leu Cys Cys
                      60
                                          65
Pro Arg Cys Pro Glu Asp Ser Leu Pro Pro Val Asn Asn Xaa Val Thr
Ser
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<210> 478 <211> 250 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<400> 478

<222> -18..**-**1

Met Arg Ile Leu Gln Leu Ile Leu Leu Ala Leu Ala Thr Gly Leu Val - 15 -10 Gly Gly Glu Thr Arg Ile Ile Lys Gly Phe Glu Cys Lys Pro His Ser 5 10 Gln Pro Trp Gln Ala Ala Leu Phe Glu Lys Thr Arg Leu Leu Cys Gly 20 25 Ala Thr Leu Ile Ala Pro Arg Trp Leu Leu Thr Ala Ala His Cys Leu 35 40 Lys Pro Arg Tyr Ile Xaa His Leu Gly Gln His Asn Leu Gln Lys Glu 50 55 Glu Gly Cys Glu Gln Thr Arg Thr Ala Thr Glu Ser Phe Pro His Pro 70 Gly Phe Asn Asn Ser Leu Pro Asn Lys Asp Xaa Xaa Asn Asp Ile Met 85 90 Leu Val Xaa Met Xaa Ser Pro Val Ser Ile Thr Trp Ala Val Arg Pro 100 105 Leu Thr Leu Ser Ser Arg Cys Val Thr Ala Gly Thr Ser Cys Leu Ile 115 120 Ser Gly Trp Gly Ser Thr Ser Ser Pro Gln, Leu Arg Leu Pro His Thr 135 130 Leu Arg Cys Ala Asn Ile Thr Ile Ile Glu His Gln Lys Cys Glu Asn 150 155 Ala Tyr Pro Gly Asn Ile Thr Asp Thr Met Val Cys Ala Ser Val Gln 165 170 Glu Gly Gly Lys Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val 180 185 Cys Asn Gln Ser Leu Gln Gly Ile Ile Ser Trp Gly Gln Asp Pro Cys 195 200 Ala Ile Thr Arg Lys Pro Gly Val Tyr Thr Lys Val Cys Lys Tyr Val 210 215 Asp Trp Ile Gln Glu Thr Met Lys Asn Asn 230

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<210> 479
<211> 151
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 479
Met Ala Ala Ser Thr Ser Met Val Pro Val Ala Val Thr Ala Ala Val
                     -15
Ala Pro Val Leu Ser Ile Asn Ser Asp Phe Ser Asp Leu Arg Glu Ile
           1
                                5
Lys Lys Gln Leu Leu Ile Ala Gly Leu Thr Arg Glu Arg Gly Leu
                          20
Leu His Ser Ser Lys Trp Ser Ala Glu Leu Ala Phe Ser Leu Pro Ala
                       35
Leu Pro Leu Ala Glu Leu Gln Pro Pro Pro Pro Ile Thr Glu Glu Asp
                   50
                              55
Ala Gln Asp Met Asp Ala Tyr Thr Leu Ala Lys Ala Tyr Phe Asp Val
     . 65
                                    70
Lys Glu Tyr Asp Arg Ala Ala His Phe Leu His Gly Cys Asn Ala Arg
              80
                                85
Lys Ala Tyr Phe Leu Tyr Met Tyr Ser Arg Tyr Leu Val Arg Ala Ile
          95
                          100
Leu Lys Cys His Ser Ala Phe Ser Glu Thr Ser Ile Phe Arg Thr Asn
   . 110 115
Gly Lys Val Lys Ser Phe Lys
<210> 480
<211> 239
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -25..-1
<400> 480
Met Pro Arg Lys Arg Lys Cys Asp Leu Arg Ala Val Arg Val Gly Leu
                  -20
                                     -15
Leu Leu Gly Gly Gly Val Tyr Gly Ser Arg Phe Arg Phe Thr Phe
Pro Gly Cys Arg Ala Leu Ser Pro Trp Arg Val Arg Xaa Gln Arg Arg
                          15
Arg Cys Glu Met Ser Thr Met Phe Ala Asp Thr Leu Leu Ile Val Phe
                      30
Ile Ser Val Cys Thr Ala Leu Leu Ala Glu Gly Ile Thr Trp Val Leu
                                     50
Val Tyr Arg Thr Asp Lys Tyr Lys Arg Leu Lys Ala Glu Val Glu Lys
Gln Ser Lys Lys Leu Glu Lys Lys Glu Thr Ile Thr Glu Ser Ala
Gly Arg Gln Cln Lys Lys Ile Glu Arg Xaa Xaa Xaa Leu Xaa
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<210> 481 <211> 208 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -92..-1 <400> 481 Met Arg Glu Pro Glumano -90 Xaa Glu Gly Leu Arg

Met Arg Glu Pro Gln Lys Arg Thr Ala Thr Ile Ala Lys Xaa Xaa Ala -90 · -85 -80 Xaa Glu Gly Leu Arg Asp Pro Tyr Gly Arg Leu Cys Gly Ser Glu His -70 Pro Arg Arg Pro Pro Glu Arg Pro Glu Glu Asp Pro Ser Thr Pro Glu -60 -55 <u>-50</u> -45 Glu Ala Ser Thr Thr Pro Glu Glu Ala Ser Ser Thr Ala Gln Ala Gln -35 -30 Lys Pro Ser Val Pro Arg Ser Asn Phe Gln Gly Thr Lys Lys Ser Leu -25 -20 -15 Leu Met Ser Ile Leu Ala Leu Ile Phe Ile Met Gly Asn Ser Ala Lys -5 Glu Ala Leu Val Trp Lys Val Leu Gly Lys Leu Gly Met Gln Pro Gly 10 Arg Xaa His Ser Ile Phe Gly Asp Pro Lys Lys Ile Val Thr Glu Xaa 25 30 Phe Val Arg Arg Gly Tyr Leu Ile Tyr Xaa Pro Val Pro Arg Xaa Ser 40 45 50 Pro Val Glu Tyr Xaa Phe Phe Trp Gly Pro Arg Ala His Val Glu Ser 60 Ser Xaa Leu Lys Xaa Xaa His Phe Val Ala Arg Val Arg Asn Arg Cys 75 Ser Lys Asp Trp Pro Cys Asn Tyr Asp Trp Asp Ser Asp Asp Asp Ala 90 95 Glu Val Glu Ala Ile Leu Asn Ser Gly Ala Xaa Gly Tyr Ser Ala Pro

110

<210> 482 <211> 86 <212> PRT <213> Homo sapiens

<221> SIGNAL <222> -39..-1 <400> 482 Met Asn Val Gly Thr Ala His Xaa Xaa Val Asn Pro Asn Thr Arg Val -30 -25 -35 Met Asn Ser Arg Gly Ile Trp Leu Ser Tyr Val Leu Ala Ile Gly Leu -20 -15 -10 Leu His Ile Val Leu Leu Ser Ile Pro Phe Val Ser Val Pro Val Val -5 1 Trp Thr Leu Thr Asn Leu Ile His Asn Met Gly Met Tyr Ile Phe Leu 10 15 20 His Thr Val Lys Gly Thr Pro Phe Glu Thr Pro Asp Gln Gly Lys Ala 30 35 Arg Leu Leu Thr His Trp 45 <210> 483 <211> 40 <212> PRT <213> Homo sapiens <220'> <221> SIGNAL <222> -27..-1

<212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -16..-1 <400> 484 Met Leu Gly Phe Phe Leu Phe Leu Ser Phe Val Leu Met Tyr Asp Gly -15 -10 - 5 Leu Arg Leu Phe Gly Ile Leu Ser Thr Cys Arg Val His His Thr Met 1 5 10 Asn Gln Phe Leu Ile Asp Ile Ser Ser Phe Thr Ser Arg Val Lys Lys 25 Lys Ile Phe Leu Phe Tyr Ala Phe Xaa Gly Cys Xaa Phe Gln Ser Ala 40 Thr

<210> 485 <211> 130

<210> 484 <211> 65 <212> PRT

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<213> Homo sapiens
<220>
<221> SIGNAL
<222> -55..-1
<400> 485
Met Ala Met Trp Asn Arg Pro Xaa Xaa Xaa Leu Pro Gln Gln Pro Leu
                            -45
Xaa Ala Glu Pro Thr Ala Glu Gly Glu Pro His Leu Pro Thr Gly Arg
                                        -25
             -35
                            -30
Xaa Xaa Thr Glu Ala Asn Arg Phe Ala Tyr Ala Ala Leu Cys Gly Ile
         -20
                         -15
                                    -10
Ser Leu Ser Gln Leu Phe Pro Glu Pro Glu His Ser Ser Phe Cys Thr
              1 5
Glu Phe Met Ala Gly Leu Val Xaa Trp Leu Glu Leu Ser Glu Ala Val
                        20
      15
Leu Pro Thr Met Thr Ala Phe Ala Ser Gly Leu Gly Gly Glu Gly Xaa
                     35
       30
Xaa Cys Val Cys Ser Asn Phe Thr Glu Gly Pro His Leu Glu Gly Arg
                  50
       4.5
Pro Asp Gly Asp His Ser Gly Pro Ser Glu Leu Leu Thr Gln Gly Trp
                        65
Ala Leu
  75
<210> 486
<211> 209
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -84..-1
<400> 486
Met Val Asn Phe Pro Gln Lys Ile Ala Gly Glu Leu Tyr Gly Pro Leu
                               -75
                                                 -70
              -80
Met Leu Val Phe Thr Leu Val Ala Ile Leu Leu His Gly Met Lys Thr
          -65
                            -60
Ser Asp Thr Ile Ile Arg Glu Gly Thr Leu Met Gly Thr Ala Ile Gly
                         -45
                                          -40
Thr Cys Phe Gly Tyr Trp Leu Gly Val Ser Ser Phe Ile Tyr Phe Leu
                     -30
                                       -25
Ala Tyr Leu Cys Asn Ala Gln Ile Thr Met Leu Gln Met Leu Ala Leu
                                   -10 -5
               -15
Leu Gly Tyr Gly Leu Phe Gly His Cys Ile Val Leu Phe Ile Thr Tyr
                                    10
                            5
Asn Ile His Leu Arg Ala Leu Phe Tyr Leu Phe Trp Leu Leu Val Gly
       15
Gly Leu Ser Thr Leu Arg Met Val Ala Val Leu Val Ser Arg Thr Val
                     35
Gly Pro Thr Xaa Arg Xaa Leu Leu Cys Gly Thr Leu Ala Ala Leu His
                  50
                                   55
Met Leu Phe Leu Leu Tyr Leu His Phe Ala Tyr His Lys Xaa Val Xaa
                                70
```

Gly Ile Leu Asp Thr Leu Glu Gly Pro Asn Ile Pro Pro Ile Gln Arg 80 85 90 Val Pro Arg Asp Ile Pro Ala Met Leu Pro Ala Ala Arg Leu Pro Thr

```
100
                                       105
      95
Thr Val Leu Asn Ala Thr Ala Lys Ala Val Ala Val Thr Leu Gln Ser
         115
His
125
<210> 487
<211> 36
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -17..-1
<400> 487
Met Gly Trp Gln Arg Trp Trp Cys Phe His Leu Gln Ala Glu Ala Ser
    -15 -10
Ala His Pro Pro Gln Gly Leu Gln Ala Gln Phe Ser Cys Cys Pro Trp
          5
                            10
Val Gly Ile Cys
<210> 488
<211> 44
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -29..-1
<400> 488
Met Met Ser Ser Glu Leu Arg Arg Asn Pro His Phe Leu Lys Ser Asn
          -25 -20
Leu Phe Leu Gln Leu Leu Val Ser His Glu Ile Val Cys Ala Thr Glu
   -10 -5
Thr Val Thr Thr Asn Phe Leu Arg His Glu Lys Ala
 5
             10
<210> 489
<211> 163
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -52..-1
<400> 489
Met Glu His Tyr Arg Lys Ala Gly Ser Val Glu Leu Pro Ala Pro Ser
                             -40
 -50
                      -45
Pro Met Pro Gln Leu Pro Pro Asp Thr Leu Glu Met Arg Val Arg Asp
 -35
                   -30
                                    -25
Gly Ser Lys Ile Arg Asn Leu Leu Gly Leu Ala Leu Gly Arg Leu Glu
-20
             -15 -10 · -5
Gly Gly Ser Ala Arg His Val Val Phe Ser Gly Ser Gly Arg Ala Ala
```

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1
                        5
Gly Lys Ala Val Ser Cys Ala Glu Ile Val Lys Arg Arg Val Pro Gly
   15 20
                             25
Leu His Gln Leu Thr Lys Leu Xaa Phe Leu Gln Thr Glu Asp Ser Trp
                  35
                            40
Val Pro Xaa Ser Pro Asp Thr Gly Leu Xaa Pro Leu Thr Val Arg Arg
45
              50
                   55 60
His Val Pro Ala Xaa Trp Val Leu Leu Xaa Arg Asp Pro Leu Asp Pro
           65
                      70
Asn Glu Cys Gly Tyr Gln Pro Pro Gly Ala Pro Pro Gly Leu Gly Ser
             85 90
Met Pro Ser Ser Cys Gly Pro Arg Ser Xaa Lys Arg Ala Xaa Xaa
                     100
Thr Arg Ser
   110
<210> 490
<211> 64
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -47..-1
<400> 490
Met His Gly Phe Glu Ile Ile Ser Leu Lys Glu Glu Ser Pro Leu Gly
                     -40
Lys Val Ser Gln Gly Pro Leu Phe Asn Val Thr Ser Gly Ser Ser Ser
- 30
                -25
                                -20
Pro Val Thr Trp Leu Gly Leu Leu Ser Phe Gln Asn Leu His Cys Phe
-15 -10
                      -5
Pro Asp Leu Pro Thr Glu Met Pro Leu Xaa Ala Lys Gly Xaa Asn Thr
      5
                         10
                                         15
<210> 491
<211> 218
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -50..-1
Met His His Gly Leu Thr Pro Leu Leu Cly Val His Glu Gln Lys
            -45
                                   -35
                      -40
Gln Gln Val Val Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala
                         -25 -20
            -30
Leu Asp Arg Tyr Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly
         -15
                      -10 -5
Ser Ala Ser Ile Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser
      1 5
                       . 10
Ser Gln Asp Leu Ser Gly Gln Thr Ala Lys Lys Tyr Ala Val Ser Ser
15 20
                         25 30
Arg His Asn Val Ile Cys Gln Leu Leu Ser Asp Tyr Lys Xaa Lys Gln
            35
                         40
                                         45
```

Xaa Leu Lys Val Ser Ser Glu Asn Ser Asn Pro Xaa Gln Asp Leu Lys

55 Leu Thr Ser Glu Glu Glu Ser Gln Arg Leu Lys Gly Ser Glu Asn Ser 70 Gln Pro Glu Glu Met Ser Gln Glu Pro Glu Ile Asn Xaa Gly Gly Asp 85 Arg Lys Val Glu Xaa Xaa Met Lys Lys His Gly Ser Xaa His Met Gly 100 105 Phe Pro Xaa Asn Leu Xaa Asn Gly Ala Thr Ala Asp Asn Gly Asp Asp 120 115 Gly Leu Ile Pro Pro Xaa Lys Xaa Xaa Thr Pro Glu Ser Xaa Gln Phe 130 135 140 Pro Asp Thr Glu Asn Glu Gln Tyr His Arg Asp Phe Ser Gly His Pro 145 150 Xaa Phe Pro Thr Thr Leu Pro Ile Lys Gln

<210> 492 <211> 216 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -15..-1

<400> 492 Met Val Cys Val Leu Val Leu Ala Ala Ala Gly Ala Val Ala Val -15 -10 -5 Phe Leu Ile Leu Arg Ile Trp Val Val Leu Arg Ser Met Asp Val Thr 10 Pro Arg Glu Ser Leu Ser Ile Leu Val Val Ala Gly Ser Gly Gly His 25 Thr Thr Glu Ile Leu Arg Leu Leu Gly Ser Leu Ser Asn Ala Tyr Ser 40 45 Pro Arg His Tyr Val Ile Ala Asp Thr Asp Glu Met Ser Ala Asn Lys 55 60 Ile Asn Ser Phe Glu Leu Xaa Arg Xaa Asp Arg Xaa Pro Ser Asn Met 75 70 Xaa Thr Lys Tyr Tyr Ile His Arg Ile Pro Xaa Ser Arg Glu Val Gln 90 Gln Ser Trp Pro Ser Thr Val Xaa Thr Thr Leu His Ser Met Trp Leu 105 Ser Xaa Pro Leu Ile His Arg Val Lys Pro Xaa Leu Val Leu Cys Asn 120 125 Gly Pro Gly Thr Cys Val Pro Ile Cys Val Ser Ala Leu Leu Leu Gly 135 140 Ile Leu Gly Ile Lys Lys Val Ile Ile Val Tyr Val Glu Ser Ile Cys 150 155 Arg Val Lys Thr Leu Ser Met Ser Gly Lys Ile Leu Phe His Leu Ser 170 165 175 Asn Tyr Phe Ile Val Gln Trp Pro Ala Leu Lys Glu Lys Tyr Pro Lys 180 185 Ser Val Tyr Leu Gly Arg Ile Val

<210> 493 <211> 134 <212> PRT

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<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 493
Met Pro Leu Gly Ala Arg Ile Leu Phe His Gly Val Phe Tyr Ala Gly
                               -10 -5
              -15
Gly Phe Ala Ile Val Tyr Tyr Leu Ile Gln Lys Phe His Ser Arg Thr
          1 5
Leu Tyr Tyr Lys Leu Ala Val Glu Gln Leu Gln Xaa His Pro Glu Ala
           20
 15
Gln Glu Ala Leu Gly Pro Pro Leu Asn Ile His Tyr Leu Lys Leu Ile
30
                35
Asp Arg Glu Asn Phe Val Asp Ile Val Xaa Ala Lys Leu Lys Ile Pro
        . 50 55
Val Ser Gly Ser Lys Ser Glu Gly Leu Leu Tyr Val His Ser Ser Arg
                           70
Gly Gly Pro Phe Gln Arg Trp His Leu Asp Glu Val Phe Leu Glu Leu
    80 85
Lys Asp Gly Gln Gln Ile Pro Val Phe Lys Leu Ser Gly Glu Asn Gly
          100
Asp Glu Val Lys Lys Glu
110
<210> 494 ·
<211> 85
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -16..-1
<400> 494
Met Ala Val Thr Ala Leu Ala Ala Xaa Thr Trp Leu Gly Val Trp Gly
               -10
                                - 5
Val Arg Thr Met Gln Ala Arg Gly Phe Gly Ser Asp Gln Ser Glu Asn
                              10
Val Asp Arg Gly Ala Gly Ser Ile Arg Glu Ala Gly Gly Ala Phe Gly
                           25
Lys Arg Glu Gln Ala Glu Glu Glu Arg Tyr Phe Arg Ala Gln Ser Thr
                      40
                                  45
Glu Gln Leu Ala Xaa Leu Lys Lys Xaa His Glu Glu Glu Ile Val His
                   55
                         . 60
His Arg Glu Gly Asp
65
<210> 495
<211> 292
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
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<222> -29..-1

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<400> 495
Met His Gly Leu Leu His Tyr Leu Phe His Thr Arg Asn His Thr Phe
             -25
                             -20
Ile Val Leu His Leu Val Leu Gln Gly Met Val Tyr Thr Glu Tyr Thr
                         -5
Trp Glu Val Phe Gly Tyr Cys Gln Glu Leu Glu Leu Ser Leu His Tyr
                 10
Leu Leu Pro Tyr Leu Leu Gly Val Asn Leu Phe Phe Thr
              25
                                30
Leu Thr Cys Gly Thr Asn Pro Gly Ile Ile Thr Lys Ala Asn Glu Leu
                           45
Leu Phe Leu His Val Tyr Glu Phe Asp Glu Xaa Met Phe Pro Lys Asn
                 60
Val Arg Cys Ser Thr Cys Asp Leu Arg Lys Pro Ala Arg Ser Xaa His
                     75
Cys Xaa Val Cys Asn Trp Cys Val His Arg Phe Xaa His His Cys Val
       . 90
                                   95
Trp Val Asn Asn Cys Ile Gly Ala Trp Asn Ile Arg Xaa Phe Leu Ile
    105
                        110
Tyr Val Leu Thr Leu Thr Ala Ser Ala Ala Thr Val Ala Ile Val Ser
                          125
            120
Thr Thr Phe Leu Val His Leu Val Val Met Ser Asp Leu Tyr Gln Glu
                         140
       135
Thr Tyr Ile Asp Asp Leu Gly His Leu His Val Met Asp Thr Val Phe
                            160
     150 155
Leu Ile Gln Tyr Leu Phe Leu Thr Phe Pro Arg Ile Val Phe Met Leu
                                   175
 165 170
Gly Phe Val Val Leu Xaa Phe Leu Leu Gly Gly Tyr Leu Leu Phe
                                190
   185
Val Leu Tyr Leu Ala Ala Thr Asn Gln Thr Thr Asn Glu Trp Tyr Arg
            200 205
Xaa Asp Trp Ala Trp Cys Gln Arg Cys Pro Leu Val Ala Trp Pro Pro
         215 220
                                           225
Ser Ala Glu Pro Gln Val His Arg Asn Ile His Ser His Gly Leu Arg
 230 235
                                       240
Xaa Asn Leu Gln Glu Ile Phe Leu Pro Ala Phe Pro Cys His Glu Arg
                 250
Lys Lys Gln Glu
260
```

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<210> 496
<211> 122
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -56..-1
<400> 496
Met Thr Gly Phe Leu Leu Pro Pro Ala Ser Arg Gly Thr Arg Arg Ser
                    -50
Cys Ser Arg Ser Arg Lys Arg Gln Thr Arg Arg Arg Asn Pro Ser
                   -35
                                      -30
Ser Phe Val Ala Ser Cys Pro Thr Leu Leu Pro Phe Ala Cys Val Pro
              -20
                               -15
Gly Ala Ser Pro Thr Thr Leu Ala Phe Pro Pro Val Xaa Leu Thr Gly
           - 5
                       1
Pro Xaa Thr Asp Gly Ile Pro Phe Ala Leu Xaa Ser Ala Ala Gly Pro
```

Phe Cys Ala Ser Phe Pro Ser Gly Xaa Leu Ser Pro Pro Gly Pro Leu 25 30 35 40

Pro Gly Val Arg Gly Leu Pro Leu Pro Ser Val Phe Tyr Ser Cys Gly 50 55

Ala His Pro Lys Val Leu Lys Val Ala Leu 60 65

<210> 497 <211> 59 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -28..-1 <400> 497 Met Leu Xaa Leu Ser Arg Ala Thr Lys Xaa Gly Arg Ala Arg Trp Leu -25 -20 Met Pro Val Ile Pro Ala Leu Gln Glu Ala Xaa Ala Gly Gly Ser Arg -5 Gly Gln Glu Phe Glu Thr Ser Leu Ala Asn Met Glu Thr Glu Ala Gly 10 Glu Leu Leu Lys Pro Arg Arg Arg Leu Gln 25

<212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -13..-1 <400> 498 Met His Leu Leu Ser Asn Trp Ala Asn Pro Ala Ser Ser Arg Arg Pro -10 -5 Ser Met Ala Ala Ser Gly Thr Ser Trp Ile Ser Ser Thr Leu Ala His 10 15 Ser Leu Ser Leu Arg Asp Val Ser Glu Arg Leu Cys Ser Cys Trp Arg 25 30 Thr Ile Ser Met Gly Pro Cys Ala Arg Gly Ser Pro Met Asn Ser Ser 40 45 Gly Val His Arg Lys Ser Ser Arg Leu Phe Tyr Ile Arg Thr Pro Met 60 Arg Arg Ser Ser Cys His Leu Glu Cys Xaa Val Ile Phe Leu Leu Gly 70 75 Arg Gln Leu 85

<210> 499 <211> 99 <212> PRT <213> Homo sapiens

<210> 498 <211> 99

<221> SIGNAL

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<220>
<221> SIGNAL
<222> -13..-1
<400> 499
Met His Leu Leu Ser Asn Trp Ala Asn Pro Ala Ser Ser Arg Arg Pro
                            - 5
Ser Met Ala Ala Ser Gly Thr Ser Trp Ile Ser Ser Thr Leu Ala His
                                  15
                     10
Ser Leu Ser Leu Arg Asp Val Ser Glu Arg Leu Cys Ser Cys Trp Arg
                                    30
                 25
Thr Ile Ser Met Gly Pro Cys Ala Arg Gly Ser Pro Met Asn Ser Ser
             40
                                45
Gly Val His Arg Lys Ser Ser Arg Leu Phe Tyr Ile Arg Thr Pro Met
                60
          55
Arg Arg Ser Ser Cys His Leu Xaa Cys Gln Val Ile Phe Leu Leu Gly
                75
      70
Arg Gln Leu
  85
<210> 500
<211> 108
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -25..-1
<400> 500
Met Ser Leu Thr Ser Ser Ser Ser Val Arg Val Glu Trp Ile Ala Ala
-25 -20
                                     -15
Val Thr Ile Ala Ala Gly Thr Ala Ala Ile Gly Tyr Leu Ala Tyr Lys
              -5
Arg Phe Tyr Val Lys Asp His Arg Asn Lys Ala Met Ile Asn Leu His
      10
                          15
Ile Gln Lys Asp Asn Pro Lys Ile Val His Ala Phe Asp Met Glu Asp
                      30
Leu Gly Asp Lys Ala Val Tyr Cys Arg Cys Trp Arg Ser Lys Lys Phe
                  45
                                     50
Pro Phe Cys Asp Gly Ala His Thr Lys His Asn Glu Glu Thr Gly Asp
              60
Asn Val Gly Pro Leu Ile Ile Lys Lys Lys Glu Thr
<210> 501
<211> 183
<212> PRT
<213> Homo sapiens
<220>
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<222> -15..-1

<400> 501

Met Glu Ala Met Trp Leu Leu Cys Val Ala Leu Ala Val Leu Ala Trp
-15 -10 -5 1

Gly Phe Leu Trp Val Trp Asp Ser Ser Glu Arg Met Lys Ser Arg Glu

```
10
Gln Gly Arg Arg Leu Gly Ala Glu Ser Arg Thr Leu Leu Val Ile Ala
                25 . 30
His Pro Asp Asp Glu Ala Met Phe Phe Ala Pro Thr Val Leu Gly Leu
                    40
                          45
Ala Arg Leu Arg His Trp Val Tyr Leu Leu Cys Phe Ser Ala Gly Asn
             55
                       60
Tyr Tyr Asn Gln Gly Glu Thr Arg Lys Lys Glu Leu Leu Gln Ser Cys
           70 75
Asp Val Leu Gly Ile Pro Leu Ser Ser Val Met Ile Ile Asp Asn Arg
              90
Asp Phe Pro Xaa Asp Pro Gly Met Gln Trp Asp Thr Xaa His Val Ala
                    105
Xaa Val Leu Leu Gln His Ile Glu Val Asn Gly Ile Asn Leu Val Val
                    120
                              125
Thr Phe Asp Ala Gly Gly Xaa Ser Gly His Ser Asn His Ile Ala Leu
130 135
                                 140
Tyr Ala Ala Val Arg Lys Leu Glu Gly Gln Ile Cys Lys Pro Cys Gly
             150
Thr Gly Gln Asp Phe Lys Glu
         165
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<210> 502

<211> 98

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -15..-1

<400> 502

Met Glu Ala Met Trp Leu Leu Cys Val Ala Leu Ala Val Leu Ala Trp
-15 -5 1

Gly Phe Leu Trp Val Trp Asp Ser Ser Glu Arg Met Lys Ser Arg Glu
5 10 15

Gln Gly Xaa Arg Leu Gly Ala Glu Ser Arg Thr Leu Leu Val Ile Ala 20 25 30

His Pro Asp Asp Glu Ala Met Phe Phe Ala Pro Thr Val Leu Gly Leu 35 40 45

Ala Arg Leu Arg His Trp Val Tyr Leu Leu Cys Phe Ser Ala Val Phe 50 55 60 65

Arg Arg Glu Leu Ser Glu Tyr Thr Glu Xaa Leu Thr Ser Glu Pro Leu 70 75 80

Xaa Ala

<210> 503

<211> 183

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -57..-1

<400> 503

Met Asp Val Thr Gly Asp Glu Glu Glu Glu Ile Lys Gln Glu Ile Asn
-55 -50 -45

Met Leu Lys Lys Tyr Ser His His Arg Asn Ile Ala Thr Tyr Tyr Gly -35 -30 Ala Phe Ile Lys Lys Asn Pro Pro Gly Met Asp Asp Gln Leu Trp Leu -20 -15 Val Met Glu Phe Cys Gly Ala Gly Ser Val Thr Asp Leu Ile Lys Asn - 5 Thr Lys Gly Asn Thr Leu Lys Glu Glu Trp Ile Ala Tyr Ile Cys Xaa 15 Glu Ile Leu Arg Gly Leu Xaa His Leu His Gln His Lys Val Ile His 30 Arg Xaa Ile Lys Gly Gln Asn Val Leu Leu Thr Glu Asn Ala Glu Val 45 Lys Leu Val Asp Phe Gly Xaa Xaa Ala Gln Leu Asp Arg Thr Val Gly Arg Xaa Asn Thr Phe Ile Gly Thr Pro Tyr Trp Met Ala Pro Xaa Val 80 Ile Ala Cys Asp Glu Asn Pro Xaa Ala Thr Tyr Asp Phe Lys Xaa Asp 95 Leu Trp Ser Leu Gly Ile Thr Ala Ile Glu Met Ala Glu Gly Leu Pro 110 Leu Ser Val Thr Cys Thr Pro

<210> 504 <211> 140 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<400> 504

<222> -14..-1

Met Phe Leu Thr Ala Leu Leu Trp Arg Gly Arg Ile Pro Gly Arg Gln -5 -10 Trp Ile Gly Lys His Arg Arg Pro Arg Phe Val Ser Leu Arg Ala Lys 10 Gln Asn Met Ile Arg Arg Leu Glu Ile Glu Ala Glu Asn His Tyr Trp 25 Leu Ser Met Pro Tyr Met Thr Arg Glu Glu Glu Arg Gly His Ala Ala 40 45 Leu Arg Arg Arg Glu Ala Phe Glu Ala Ile Lys Ala Ala Ala Thr Ser 60 55 Lys Phe Pro Pro His Arg Phe Ile Ala Asp Gln Leu Asp His Leu Asn 75 Xaa His Gln Glu Met Val Leu Ile Leu Ser Arg His Pro Trp Ile Leu 90 Trp Ile Thr Glu Leu Thr Ile Phe Thr Trp Ser Gly Leu Lys Asn Cys 105 Ser Leu Cys Glu Asn Glu Leu Trp Thr Ser Leu Tyr 120

<210> 505 <211> 59 <212> PRT <213> Homo sapiens

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<221> SIGNAL
<222> -14..-1
<400> 505
Met Ala Ala Leu Val Thr Val Leu Phe Thr Gly Val Arg Arg Leu His
        -10
                      -5
Cys Ser Ala Xaa Leu Gly Arg Ala Ala Ser Gly Xaa Tyr Ser Arg Asn
                     10 15
Trp Leu Pro Thr Pro Pro Ala Thr Gly Pro Leu Pro Ser Ser Gln Thr
        25
Gly His Met Arg Met Ala Ala Leu Leu Pro Gln
      40
<210> 506
<211> 101
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -36..-1
<400> 506
Met Gly Pro Tyr Asn Val Ala Val Pro Ser Asp Val Ser His Ala Arg
  -35 -30 -25
Phe Tyr Phe Leu Phe His Arg Pro Leu Arg Leu Leu Asn Leu Leu Ile
                               -10 . -5
-20 -15
Leu Ile Glu Gly Ser Val Val Phe Tyr Gln Leu Tyr Ser Leu Leu Arg
                5
                              10
            1
Ser Glu Lys Trp Asn His Thr Leu Ser Met Ala Leu Ile Leu Phe Cys
            20
   15
Asn Tyr Tyr Val Leu Phe Lys Leu Leu Arg Asp Arg Xaa Xaa Leu Gly
          35
                          40
Arg Ala Tyr Ser Tyr Pro Leu Asn Ser Tyr Glu Leu Lys Ala Asn Xaa
                       55
Ala Ala Ser Xaa Gln
<210> 507
<211> 341
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -55..-1
<400> 507
Met Arg Lys Val Val Leu Ile Thr Gly Ala Ser Ser Gly Ile Gly Leu
       -50
                                -45
Ala Leu Cys Lys Arg Leu Leu Ala Glu Asp Asp Glu Leu His Leu Cys
                             -30
            -35
Leu Ala Cys Arg Asn Met Ser Lys Ala Glu Ala Val Cys Ala Ala Leu
```

-15 Leu Ala Ser His Pro Thr Ala Glu Val Thr Ile Val Gln Val Asp Val

Ser Asn Leu Gln Ser Phe Phe Arg Ala Ser Lys Glu Leu Lys Gln Arg

1

5

20

-20

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```
Phe Gln Arg Leu Asp Cys Ile Tyr Leu Asn Ala Gly Ile Met Pro Asn
                                35
Pro Gln Leu Asn Ile Lys Ala Leu Phe Phe Gly Leu Phe Ser Arg Lys
                             50
Val Ile His Met Phe Ser Thr Ala Glu Gly Leu Leu Thr Gln Gly Asp
Lys Ile Thr Ala Asp Gly Leu Gln Glu Val Phe Glu Thr Asn Val Phe
                            85
                     80
Gly His Phe Ile Leu Ile Arg Glu Leu Glu Pro Leu Cys His Ser
                95
                                    100
Asp Asn Pro Ser Gln Leu Ile Trp Thr Ser Ser Arg Ser Ala Arg Lys
                                115 120
       110
Ser Asn Phe Ser Leu Glu Asp Phe Gln His Ser Lys Gly Lys Glu Pro
                             130
                                               135
Tyr Ser Ser Ser Lys Tyr Ala Thr Asp Leu Leu Ser Val Ala Leu Asn
                                           150
                         145
Arg Asn Phe Asn Gln Gln Gly Leu Tyr Ser Asn Val Ala Cys Pro Gly
                    160
                                       165
Thr Ala Leu Thr Asn Leu Thr Tyr Gly Ile Leu Pro Pro Phe Ile Trp
                175
                                    180
Thr Leu Leu Met Pro Ala Ile Leu Leu Leu Arg Phe Phe Ala Asn Ala
                                195
             190
Phe Thr Leu Thr Pro Tyr Asn Gly Thr Glu Ala Leu Val Trp Leu Phe
                                 215
          205
                            210
His Gln Lys Pro Glu Ser Leu Asn Pro Leu Ile Lys Tyr Leu Ser Ala
                        225
                                           230
Thr Thr Gly Phe Gly Arg Asn Tyr Ile Met Thr Gln Lys Met Asp Leu
                     240
                                       245
Asp Glu Asp Thr Ala Glu Lys Phe Tyr Gln Lys Leu Leu Glu Leu Glu
                 255
                                   260
Lys His Ile Arg Val Thr Ile Gln Lys Thr Asp Asn Gln Ala Arg Leu
             270
                              275
Ser Gly Ser Cys Leu
          285
```

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<210> 508
<211> 108
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -42..-1
<400> 508
Met His Ile Leu Gln Leu Leu Thr Thr Val Asp Asp Gly Ile Gln Ala
                          -35
Ile Val His Cys Pro Asp Thr Gly Lys Asp Ile Trp Asn Leu Leu Phe
                      -20
                                         -15
Asp Leu Val Cys His Glu Phe Cys Gln Ser Asp Asp Pro Ala Ile Ile
              - 5
                                     1
Leu Gln Xaa Gln Lys Thr Val Leu Ala Ser Val Phe Ser Val Leu Ser
                             15
Ala Ile Tyr Ala Ser Gln Thr Glu Gln Xaa Tyr Leu Lys Ile Xaa Lys
                         30
                                  35
Gly Asp Gly Gly Ser Gly Ser Lys Gly Arg Pro Xaa Xaa Gln Thr Glu
                      45
Xaa Phe Leu Cys Ile Ser Lys Pro Ser Ser Phe Leu
```

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<210> 509
<211> 80
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1
<400> 509
Met Glu Glu Ile Ser Ser Pro Leu Val Glu Phe Val Lys Val Leu Cys
                      -20
                                         -15
Thr Asn Gln Val Leu Ile Thr Ala Arg Ala Val Pro Thr Lys Lys Ala
                - 5
                                     1
Ser Val Arg Cys Val Glu Lys Arg Phe Trp Ile Pro Lys Thr Thr Ser
          10
                              15
Lys His Leu Ser Arg Cys Ile Asp Gly Ile Ser Gly Phe Leu Asn Asp
                       30
                                            35
Phe Thr Phe Cys Leu Glu Phe Ser Arg His Arg Cys Gln Leu Thr Glu
                      45
<210> 510
<211> 158
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -44..-1
<400> 510
Met Ala Gly Phe Leu Asp Asn Phe Arg Trp Pro Glu Cys Glu Cys Ile
           -40 -35 -30
Asp Trp Ser Glu Arg Arg Asn Ala Val Ala Ser Val Val Ala Gly Ile
                             -20
Leu Phe Phe Thr Gly Trp Trp Ile Met Ile Asp Ala Ala Val Val Tyr
                      - 5
Pro Lys Pro Glu Gln Leu Asn His Ala Phe His Thr Cys Gly Val Phe
               10
Ser Thr Leu Ala Phe Phe Met Ile Asn Ala Val Ser Asn Ala Gln Val
                                 30
Arg Gly Asp Ser Tyr Glu Ser Gly Cys Leu Gly Arg Thr Gly Ala Arg
                             45
Val Trp Leu Phe Ile Gly Phe Met Leu Met Phe Gly Ser Leu Ile Ala
                       60
Ser Met Trp Ile Leu Phe Gly Ala Tyr Val Thr Gln Asn Thr Asp Val
                     75
                                      80
Tyr Pro Gly Leu Ala Val Phe Phe Gln Asn Ala Leu Ile Phe Phe Ser
```

95

110

Thr Leu Ile Tyr Lys Phe Gly Arg Thr Glu Glu Leu Trp Thr

<210> 511 <211> 130 <212> PRT <213> Homo sapiens

90

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<220>
 <221> SIGNAL
 <222> -28..-1
 <400> 511
 Met Asn Trp Glu Leu Leu Trp Leu Leu Val Leu Cys Ala Leu Leu
           -25
                               -20
 Leu Leu Val Gln Leu Leu Arg Phe Leu Arg Ala Asp Gly Asp Leu
                         -5
 Thr Leu Leu Trp Ala Glu Trp Gln Gly Arg Arg Pro Glu Trp Glu Leu
                                      15
                   10
 Thr Asp Met Val Val Trp Val Thr Gly Ala Ser Ser Gly Ile Gly Glu
                25
                                  30
 Glu Leu Ala Tyr Gln Leu Ser Lys Leu Gly Val Ser Leu Val Leu Ser
                              45
 Ala Arg Arg Val His Glu Leu Glu Arg Val Lys Arg Arg Cys Leu Glu
                           60
 Asn Gly Asn Leu Lys Glu Lys Asp Ile Leu Val Leu Pro Leu Asp Leu
                     75
                                        80
. Thr Asp Thr Gly Ser His Glu Ser Gly Tyr Gln Ser Cys Ser Pro Gly
 Ile Trp
 <210> 512
 <211> 199
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -62..-1
 <400> 512
 Met Ser Gln Arg Ser Leu Cys Met Asp Thr Ser Leu Asp Val Tyr Arg
                           -55
 Xaa Leu Ile Glu Leu Asn Tyr Leu Gly Thr Val Ser Leu Thr Lys Cys
                       -40
                                          -35
 Val Leu Pro His Met Ile Glu Arg Lys Gln Gly Lys Ile Val Thr Val
                   -25
                                      -20
 Asn Ser Ile Leu Gly Ile Ile Ser Val Pro Leu Ser Ile Gly Tyr Cys
               -10 -5
 Ala Ser Lys His Ala Leu Arg Gly Phe Phe Asn Gly Leu Arg Thr Glu
                          10
 Leu Ala Thr Tyr Pro Gly Ile Ile Val Ser Asn Ile Cys Pro Gly Pro
                      25
 Val Gln Ser Asn Ile Val Glu Asn Ser Leu Ala Gly Glu Val Thr Lys
```

Thr Ile Gly Asn Asn Gly Asn Gln Ser His Lys Met Thr Thr Ser Arg

45

60

Ile Phe Lys Thr Lys His Asp

135

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<210> 513
<211> 180
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -25..-1
<400> 513
Met Asn Thr Val Leu Ser Arg Ala Asn Ser Leu Phe Ala Phe Ser Leu
      -20
                        -15
Ser Val Met Ala Ala Leu Thr Phe Gly Cys Phe Ile Xaa Thr Ala Phe
       · -5
                               1
Lys Asp Arg Ser Val Pro Val Arg Leu His Val Ser Arg Ile Met Leu
      10
                     15
Lys Asn Val Glu Asp Phe Thr Gly Pro Arg Glu Arg Ser Asp Leu Gly
             30
Phe Ile Thr Phe Asp Ile Thr Ala Asp Leu Glu Asn Ile Phe Asp Trp
                     50
              45
Asn Val Lys Gln Leu Phe Leu Tyr Leu Ser Ala Glu Tyr Ser Thr Lys
                               65
Asn Asn Ala Leu Asn Gln Xaa Val Leu Trp Asp Lys Ile Val Leu Arg
Gly Asp Asn Pro Lys Leu Leu Leu Lys Asp Met Lys Thr Lys Tyr Phe
                            .. 100
Phe Phe Asp Asp Gly Asn Gly Leu Xaa Gly Asn Arg Asn Val Thr Leu
                 110
Thr Leu Ser Trp Asn Val Val Pro Asn Ala Gly Ile Leu Pro Leu Val
120 125
                     130
Thr Gly Ser Gly His Val Ser Val Pro Phe Pro Asp Thr Tyr Glu Ile
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Thr Lys Ser Tyr
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